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STUDIES ON THE DESTRUCTION OF RED BLOOD CELLS*

III. Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns: Spherocytosis and Increased Osmotic Fragility of Red Blood Cells

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HEMOGLOBINURIA, the excretion of extracellular hemoglobin in the urine, is recognized as an early complication of severe thermal burns. It is a sign of rapid destruction of red blood cells producing, in the plasma, free hemoglobin, which is usually excreted promptly by the kidney.[1–3] In this paper observations are reported on the changes in the blood and in the urine and on the kidney complications occurring in 14 patients with moderate or severe thermal burns, 10 of whom showed hemoglobinuria. Experimental studies on the effect of heating human red cells and on the effect of injection into the dog of heated canine red cells will be outlined briefly and reported in more complete form elsewhere.

In the literature on thermal burns, hemoglobinuria has infrequently been reported as a complication of severe third-degree burns involving usually half or more of the body surface.[4–6] Cope and Rhinelander[7] reported 9 cases of hemoglobinuria in patients burned in the Cocoanut Grove disaster. Hemoglobinuria, according to Wilms,[6] was not a constant finding in severe burns. It lasted for only one or two days, and the amount of blood destroyed was not sufficient to endanger the patient's life. Oliguria and albuminuria, however, were the usual consequences of severe second-degree or third-degree burns, whether or not hemoglobinuria was present. Albuminuria lasted five days or longer. Marchand[8] in a critical review of the pathology of thermal burns found that the renal lesion of so-called "burn nephritis" is similar to that produced by hemoglobinuria due to other causes. Experimentally, hemoglobinuria has been demonstrated in animals burned by scalding.[9, 10] The heating of blood to 52 to 65°C. in vitro[9–15] and the apparent heating of blood in vivo in burned animals[10, 16–19] have both produced progressive fragmentation of the red cells, with the formation of spherocytes and microspherocytes. Pfeiffer[19] found that destruction of erythrocytes by heat was evidenced by the immediate occurrence of hemoglobin in the plasma of anesthetized animals burned by scalding, with a rise in subcutaneous temperature as high as 63°C. Von Lesser[10] observed hemoglobinemia and hemoglobinuria in burned animals, in normal animals transfused with blood from a burned animal, and in normal animals injected with homologous blood heated to 60 or 62°C. in vitro. The red cells with abnormal morphology were rapidly removed from the animal's circulation and presumably destroyed. Spiegler[12] and Isaacs, Brock and Minot[15] confirmed the morphologic changes occurring in heated blood and observed that red cells heated to above 50°C. were increased in osmotic fragility. No hemolysins or agglutinins were found in the plasma or serum of burned animals by Burkhardt.[13] Spiegler noted the lack of toxic manifestations when heated blood was injected into a dog.

METHODS OF INVESTIGATION

Following the Cocoanut Grove disaster, samples of urine showing hemoglobinuria were obtained for analysis. It was impossible in many cases to secure complete urine specimens during the first forty-eight hours because of incontinence, and because of the complex nurs-

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TABLE 1. *Observations on 14 Patients with Moderate or Severe Thermal Burns, of Whom 10 Showed Hemoglobinuria.*

CASE No.	HOSPITAL No.	SOURCE OF BURN	AGE	SEX	PERIOD OF SURVIVAL AFTER BURN	AREA OF BODY BURNED			INTERVAL AFTER BURN
						TOTAL BURN	SECOND DEGREE	THIRD DEGREE	
			yr.			%	%	%	
1	1088982	Cocoanut Grove	45	M	25 hr.	65			20 hr.
2	1088948	Cocoanut Grove	33	F	29 hr.	65			26 hr.
3	1088889	Cocoanut Grove	50	M	42 hr.	45			37 hr.
4	1088920	Cocoanut Grove	29	F	79 hr.	50			22 hr. 36 hr. 60 hr.
5	1088885	Cocoanut Grove	25	M	5½ d.	45	15	30	44 hr. 63 hr. 88 hr.
6	1088965	Cocoanut Grove	35	F	8½ d.	65	30	35	36 hr. 3 d. 4 d. 5 d. 6 d. 7 d.
7	1088943	Cocoanut Grove	29	F	13 d.	45	15	30	18 hr. 36 hr. 3 d. 4 d. 5 d. 6 d. 7 d. 9 d. 10 d. 11 d. 12 d.
8	1088892	Cocoanut Grove	22	M	Living	55	10	45	36 hr. 4 d. 5 d. 7 d. 9 d. 10 d. 16 d. 21 d.
9	1094717	In bed	50 (?)	F	5 hr.	30	5	25	2 hr.
10	1091461	Explosion of oil stove	40	F	5 d.	20			30 hr. 46 hr. 66 hr.
11	113422	In bed	32	M	9 d.		3	17	2 hr. 11 hr. 32 hr. 3 d. 6 d.
12	1091512	In bed	32	F	28 d.	65	20	45	3 hr. 10 hr. 25 hr. 34 hr. 50 hr. 74 hr.
13	1094057	In bed	50	M	32 d.	55	10	45	38 hr.
14	1103634	In dwelling	37	F	Living	15	3	12	½ hr. 2 hr. 3 hr. 4½ hr. 5 hr. 13 hr. 17 hr. 37 hr. 3 d. 5 d. 9 d. 9 d. 17 d.

TABLE 1 *(continued)*.

CASE NO.	DEGREE OF INCREASE ABOVE NORMAL	OSMOTIC FRAGILITY OF RED CELLS — DEGREE OF HEMOLYSIS							SPHEROCYTES	
		1%	2.5%	5%	10%	50%	75%	95%	INTERVAL AFTER BURN	PER CENT
		% NaCl	% NaCl	% NaCl	% NaCl	% NaCl	% NaCl	% NaCl		
1	+	0.63	0.56	0.54	0.51	0.45	0.43	0.40		
2	+ +	0.67	0.59	0.53	0.47	0.39	0.35	0.29		
3	±	0.56	0.47	0.43	0.41	0.36	0.33	0.29	36 hr.	3.0
4	+ +	0.67	0.63	0.58	0.52	0.42	0.41	0.40		
	+	0.59	0.53	0.49	0.45	0.40	0.38	0.34	36 hr.	11.0
	+	0.59	0.53	0.47	0.43	0.38	0.35	0.29	60 hr.	9.0
5	+	0.59	0.56	0.52	0.48	0.40	0.36	0.25	2 d.	1.0
	0	0.47	0.45	0.44	0.43	0.40	0.37	0.26	3 d.	0.8
	0	0.49	0.47	0.45	0.43	0.39	0.36	0.25		
6	0	0.45	0.43	0.42	0.41	0.37	0.35	0.29	2 d.	0.2
	0	0.45	0.43	0.42	0.41	0.37	0.34	0.27		
	0	0.47	0.44	0.43	0.41	0.37	0.35	0.31	6 d.	1.2
	0	0.48	0.47	0.45	0.44	0.38	0.34	0.29		
	0	0.45	0.43	0.42	0.40	0.34	0.29	0.25		
	0	0.47	0.45	0.43	0.42	0.34	0.31	0.25		
7	±	0.55	0.50	0.46	0.44	0.39	0.35	0.23	4 d.	1.3
	0	0.48	0.44	0.43	0.42	0.38	0.35	0.29	5 d.	0.8
	0	0.44	0.41	0.40	0.39	0.35	0.33	0.29	6 d.	1.6
	0	0.46	0.44	0.43	0.42	0.37	0.34	0.29	8 d.	0.8
	0	0.49	0.48	0.45	0.43	0.40	0.37	0.33		
	0	0.49	0.47	0.46	0.44	0.40	0.37	0.29		
	0	0.50	0.48	0.45	0.43	0.38	0.35	0.29		
	0	0.50	0.48	0.44	0.43	0.39	0.35	0.21		
	0	0.48	0.45	0.44	0.42	0.37	0.34	0.28		
	0	0.46	0.44	0.43	0.41	0.35	0.32	0.25		
	0	0.49	0.44	0.42	0.40	0.34	0.30	0.19		
8	0	0.52	0.48	0.44	0.43	0.39	0.36	0.29	36 hr.	1.9
	0	0.48	0.46	0.45	0.43	0.38	0.35	0.25	3 d.	0.9
	0	0.48	0.46	0.44	0.43	0.38	0.35	0.28	4 d.	0.4
	0	0.47	0.44	0.43	0.43	0.40	0.38	0.30	8 d.	0.6
	0	0.48	0.46	0.44	0.43	0.39	0.35	0.33	9 d.	1.0
	0	0.48	0.46	0.44	0.43	0.40	0.37	0.28	5 mo.	1.0
	0	0.48	0.46	0.44	0.43	0.40	0.37	0.29		
	0	0.49	0.47	0.45	0.43	0.40	0.37	0.32		
9	+ + + +	0.85	0.80	0.76	0.70	0.45	0.43	0.35		
10	0	0.45	0.44	0.42	0.40	0.39	0.33	0.26	4 d.	1.2
	0	0.44	0.40	0.38	0.36	0.33	0.29	0.23		
	0	0.43	0.41	0.40	0.38	0.34	0.31	0.26		
11	0	0.48	0.45	0.43	0.42	0.38	0.34	0.26	2 hr.	1.6
	0	0.50	0.47	0.45	0.43	0.38	0.35	0.29	4 d.	1.3
	0	0.48	0.46	0.45	0.43	0.38	0.34	0.27	6 d.	2.1
	0	0.48	0.44	0.43	0.40	0.37	0.33	0.26		
	0	0.43	0.41	0.40	0.39	0.34	0.31	0.23		
12	+	0.59	0.52	0.49	0.47	0.41	0.38	0.28	8 d.	1.9
	+	0.63	0.55	0.51	0.50	0.44	0.41	0.34		
	±	0.53	0.51	0.49	0.48	0.42	0.40	0.30	20 d.	1.6
	±	0.54	0.50	0.47	0.46	0.40	0.38	0.29		
	0	0.51	0.47	0.46	0.44	0.40	0.37	0.29		
	0	0.51	0.44	0.43	0.42	0.40	0.38	0.29		
13	0	0.49	0.47	0.45	0.43	0.39	0.36	0.28	1 hr.	3.0
									9 d.	0.6
									26 d.	0.8
14	+ +	0.71	0.63	0.47	0.43	0.38	0.35	0 32	1½ hr.	4.5
	+ +	0.68	0.57	0.45	0.42	0.38	0.35	0.29	3 hr.	5.4
	± ±	0.59	0.46	0.43	0.40	0.37	0.34	0.28	4 hr.	2.8
	± ±	0.59	0.46	0.43	0.42	0.37	0.34	0.29	6 hr.	2.6
	± ±	0.59	0.48	0.42	0.41	0.37	0.34	0.29	7 hr.	5.3
	0	0.52	0.47	0.45	0.43	0.39	0.35	0.25	14 hr.	3.3
	0	0.49	0.46	0.44	0.43	0.40	0.37	0.34	17 hr.	3.5
	0	0.48	0.44	0.43	0.42	0.37	0.35	0.29	37 hr.	2.0
	0	0.48	0.45	0.43	0.42	0.36	0.34	0.26	2 d.	0.7
	0	0.45	0.43	0.41	0.40	0.35	0.33	0.23	3 d.	1.6
	0	0.45	0.43	0.40	0.40	0.35	0.32	0.25	4 d.	1.5
	0	0.48	0.46	0.44	0.43	0.37	0.34	0.29	5 d.	0.9
	0	0.47	0.45	0.44	0.42	0.38	0.35	0.29	6 d.	0.7

TABLE 1 *(continued)*.

CASE NO.	URINALYSIS	HEMOGLOBINURIA: DEGREE IN URINE	HEMOGLOBINURIA: KIDNEY FINDINGS AT AUTOPSY
1	*10 hr.*: red. *18 hr.*: brown; hemoglobin,* 90 mg. per 100 cc.; pH 5.4; 130 cc.; specific gravity, 1.012; sediment — precipitate of hemoglobin, hemoglobin casts, trace of hemosiderin.	Severe	No autopsy
2	*24 hr.* (catheterized): dark brown; scanty amount; protein, +++; sediment — no red cells.	Severe	No autopsy
3	*16 hr.*: brown; pH 5.5; specific gravity, 1.022; protein, ++; sediment — innumerable hemoglobin casts, no red cells.	Moderate	No autopsy
4	*16 hr.*: dark red; hemoglobin,* 520 mg. per 100 cc.; pH 5.5; 265 cc.; specific gravity, 1.016; protein, +++; sediment — precipitate of hemoglobin, hemoglobin casts, hemosiderin ++. *46 hr.*: light brown; hemoglobin,* 80 mg. per 100 cc.; pH 7.5; 40 cc.; specific gravity, 1.011; protein, +++; sediment — precipitate of hemoglobin, hemoglobin casts, hemosiderin ++.	Severe	Extensive hemoglobinuria; nephrosis.
5	*17 hr.*: dark red. *20 hr.*: brown. *42 hr.*: yellow; no hemoglobin; pH 5.8; 70 cc.; specific gravity, 1.014; protein +; sediment — no hemoglobin casts, hemosiderin +.	Moderate	Slight hemoglobinuria
6	*24 hr.*: black. *40 hr.*: amber; no hemoglobin; pH 4.5; protein, ++; sediment — hemoglobin casts, hemosiderin ++.	Severe	Hemoglobinuria: interstitial nephritis; healing tubular nephritis.
7	*16 hr.*: dark brown; hemoglobin,* 80 mg. per 100 cc.; pH 5.1; 190 cc.; specific gravity, 1.010; protein, ++; sediment — precipitate of hemoglobin, hemoglobin casts, hemosiderin ++.	Severe	Slight hemoglobinuria; late tubular nephritis; slight interstitial nephritis.
8	*13 hr.*: dark red. *34 hr.*: amber; trace of hemoglobin*; pH 5.8; protein, +, sediment — hemoglobin casts, hemosiderin +.	Severe	
9	*2 hr.* (catheterized): orange; trace of hemoglobin*; pH 5.5; 15 cc.; sediment — negative for hemoglobin casts, trace of hemosiderin, no red cells.	Slight	Slight hemoglobinuria
10	*24 hr.*: dark amber; trace of hemoglobin*; pH 7.0; 95 cc.; specific gravity, 1.010; protein, +++; sediment — no hemoglobin casts or hemosiderin. *44 hr.*: orange; faint trace of hemoglobin*; pH 7.0; specific gravity, 1.008; protein, ++.	Slight	Hemoglobinuria; slight nephrosis and interstitial nephritis.
11	*6 hr.*: orange; questionable trace of hemoglobin; pH 7.0†; protein, +; sediment — no hemoglobin casts, no hemosiderin. *11 hr.*: amber; negative for hemoglobin; pH 7.0; protein, ++; sediment — no hemoglobin casts, hemosiderin +.	None	No hemoglobinuria or renal abnormality
12	*8 hr.* (catheterized): yellow; no hemoglobin; pH 8.0†; 6 cc. *10 hr.* (catheterized): amber; trace of hemoglobin; pH 7.0; 190 cc.; specific gravity, 1.015; protein, +++; sediment — no hemoglobin casts, no hemosiderin, many red cells.	None	No hemoglobinuria or renal abnormality
13	*24 hr.*: yellow; no hemoglobin; acid; 440 cc.; specific gravity, 1.020; protein, +; sediment — no casts. *48 hr.*: red brown; acid; specific gravity, 1.022; 1020 cc.; sediment — many red cells and sulfadiazine crystals.	None	No hemoglobinuria or renal abnormality
14	*4 hr.*: yellow; no hemoglobin; acid†; 65 cc.; protein, +; sediment — no hemoglobin casts, hemosiderin +, few red cells (menstruation). *13 hr.*: amber; trace of hemoglobin; slightly acid; protein, +++; sediment — no hemoglobin casts, hemosiderin ++, few red cells.	None	

*Positive reaction to benzidine: no red cells in sediment.

†Received intravenous sodium lactate or sodium bicarbonate solution or both, on admission and for 24 to 48 hours.

TABLE 1 *(concluded).*

Case No.	Venous Blood: Interval after burn	Venous Blood: Hematocrit	Venous Blood: Hemoglobin	Nonprotein Nitrogen: Interval after burn	Nonprotein Nitrogen: Level	Surface Treatment of Burn	Plasma Administered: Amount	Plasma Administered: Interval after burn	Sulfonamide Therapy	Respiratory Complications§
	hr.	%	%		*mg./100 cc.*		*units‡*	*hr.*		
1	20	39	90			Débridement; triple dye.	17	21	None	+++
2	14		111			Boric ointment; triple dye.	12	30	Sodium sulfadiazine, intravenous (begun at 27 hr.)	+++
3	13		130			Débridement; tannic acid and silver nitrate.	17	42	None	++++
	25		107							
	36	43	83							
4	16	47	105			Soap - and - water cleaning; boric ointment; tannic acid and silver nitrate.	26	39	Sodium sulfadiazine, intravenous (begun at 46 hr.)	++++
	36	43	96	36 hr.	87					
	60	37	84							
5	14		115	36 hr.	71	Soap - and - water cleaning; boric ointment; triple dye; tannic acid and silver nitrate.	13	40	Sulfadiazine, oral (begun at 36 hr.)	+++
	29		122							
	33		99	3 d.	48					
	41		100							
	59		88	4 d.	62					
6	40	42	90	64 hr.	56	Boric ointment; triple dye; sulfanilamide powder.	30	48	Sodium sulfadiazine, intravenous (begun at 41 hr.)	+++
				3 d.	89					
	60	35	75	4 d.	95					
				5 d.	86					
				6 d.	92					
				7 d.	98					
7	23	46	115	36 hr.	48	Soap - and - water cleaning; triple dye.	11	24	Sodium sulfadiazine, intravenous (begun at 36 hr.)	++++
				3 d.	76					
	36	53	108	4 d.	63					
				5 d.	68					
	63	31	62	6 d.	76					
				7 d.	73					
				8 d.	71					
				9 d.	86					
				10 d.	65					
				11 d.	75					
				12 d.	75					
8	12	56	127	36 hr.	64	Boric ointment; triple dye.	17	24	Sodium sulfadiazine, intravenous (begun at 60 hr.)	+
				4 d.	42					
	36	53	111	5 d.	47					
				6 d.	37					
	64		92	8 d.	30					
				9 d.	33					
				11 d.	22					
				30 d.	17					
				3 mo.	18					
				5½ mo.	14					
9	2	45	109	2 hr.	36	None	9	4	Sodium sulfadiazine, intravenous (begun at 2½ hr.)	++++ (lobar pneumonia)
	3	40	97							
	4	35	82							
10	6	49	96	23 hr.	56	Débridement; tannic acid and silver nitrate; vaseline strips.	9	12	None	0
	8	47	96	34 hr.	56					
	23		98	50 hr.	73					
	34	33	70	55 hr.	81					
	50	36	74	3 d.	90					
				4 d.	126					
11	2	45	95	2 hr.	31	Plaster cast on arms; vaseline dressings elsewhere.	20	48	Sulfadiazine, oral (begun at 12 hr.)	+
	4	42	88	11 hr.	39					
	11	51	104	36 hr.	25					
	14	46	91	61 hr.	34					
	17	45	90	3 d.	25					
	25	42	84	4 d.	23					
	36	41	80	5 d.	44					
	61	42	78	7 d.	41					
				8 d.	84					
12	1	50	100	1 hr.	18	Débridement; triple dye.	17	11	Sulfadiazine, oral (begun at 4 d.)	0
	2	42	87	18 hr.	24					
	7	36	83	34 hr.	19					
	18	49	99	52 hr.	29					
	27	46	92	8 d.	14					
	34	43	80	16 d.	22					
	52	44	85	22 d.	29					
				27 d.	35					
13	1	43	90	1 hr.	19	Débridement; vaseline dressing on upper extremities; tannic acid and silver nitrate elsewhere.	17	42	Sulfadiazine, oral (begun at 10 hr.)	0
	4	43	87	13 hr.	40					
	7	45	95	24 hr.	49					
	13	62	125	36 hr.	59					
	17	61	124	60 hr.	32					
	18	42	99	4 d.	37					
	25	45	93	7 d.	34					
	38	55	113	11 d.	25					
	49	44	93	18 d.	29					
	60	43	88	30 d.	31					
14	1½	38	86	1½ hr.	25	Plaster cast on left arm; triple dye on thigh; bentonite (aluminum silicate) to left leg.	6	5	Sodium sulfadiazine, intravenous (begun at 12 hr.)	+ +
	2	39	83	14 hr.	35					
	7	37	78	38 hr.	51					
	14	44	101	62 hr.	41					
	38	39	82	3 d.	22					
	62	33	71	5 d.	25					
				11 d.	30					
				16 d.	31					
				23 d.	27					

‡One unit equals 250 cc.

§Respiratory-tract involvement graded as follows: slight (+); moderate (++); severe (+++); and very severe (++++).

ing problem presented by the many gravely ill patients. The urine data for Cases 1–8 in Table 1 are therefore necessarily incomplete concerning the total output of urine and the analysis of all specimens. In these cases one or more urine samples voided within sixteen to forty-two hours after the burn were examined critically. The pH and hemoglobin content were determined within a day after obtaining the specimen. Careful study of the sediment was not done until five days after collection of the early specimens, which were preserved in an icebox and remained acid and remarkably free from bacterial contamination. In the patients not injured at Cocoanut Grove (Cases 9–14), the collection and examination of urine was prompt and was more complete than in the Cocoanut Grove cases. Samples of venous blood were always examined within two hours after collection. The hematologic and chemical methods employed in this investigation have been described in detail in a previous paper.[20]

Quantitative estimation of the *hemoglobin* in plasma and in urine was performed by the benzidine method of Bing and Baker.[21, 22] Examination of *pigments* in plasma, serum or urine was made with the Hardy recording spectrophotometer.*[23] The *pH* of urine was measured with a glass electrode. The *total protein* in urine, including hemoglobin and other proteins, was roughly estimated by observing the precipitate in a sample boiled after acidification with acetic acid. *Hemosiderin* was detected microscopically as black-staining particles in a drop of sediment from centrifuged urine observed after the addition of a drop of ammonium sulfide solution.[24] Blood samples were taken from the antecubital vein or femoral vein, using as anticoagulant a mixture of dry ammonium and potassium oxalate, 200 mg. per 100 cc. of blood.[25] The *hemoglobin* was determined by a photoelectric-cell colorimeter calibrated so that 100 per cent hemoglobin was equivalent to 15.6 gm. per 100 cc. The erythrocytic volume per cent or *hematocrit* was determined by the Wintrobe[26] method.

The number of unusually *spherical cells* present in the red-cell population was estimated from fixed smears of blood stained with Wright's stain. A cell was considered to be a spherocyte if it was small in diameter compared to the other red cells and was homogeneous and intensely stained. Using these crude criteria, several observers agreed within 0.5 to 1.0 per cent on the number of spherocytes in 1000 red cells counted if the number was 3 per cent or above. In smears from 16 normal subjects the number of red cells classified as spherocytes varied from zero to 0.4 per cent, with an average value of 0.2 per cent.

The *osmotic fragility* of red cells was determined from freshly drawn venous blood. Accurately measured 0.1-cc. samples of blood were pipetted into a series of tubes containing 1.0-cc. amounts of the following solutions: hypertonic sodium chloride (2.0, 1.5 and 1.0 per cent), isotonic sodium chloride (0.85 per cent), hypotonic sodium chloride (0.80 to 0.10 per cent) and distilled water. These reagents were maintained as stock solutions kept at room temperature. The samples were mixed and centrifuged, the supernatant fluid was poured into a separate set of clean tubes, and 0.5-cc. samples of the supernatant solutions were diluted to 10 cc. with distilled water in Evelyn colorimeter tubes. One drop of ammonium hydroxide was added to each tube, the sample mixed, and the hemoglobin determined in an Evelyn colorimeter using filter No. 540. The colorimetric values observed in the hypertonic salt mixtures were averaged as the "blank" and subtracted from each value obtained in the hypotonic range to give a corrected figure for hemolysis. The percentage hemolysis at each salt concentration was then calculated by dividing the corrected figure for hemolysis by the similarly corrected figure for complete hemolysis produced in distilled water. The curve of osmotic fragility was next plotted, using the hemolysis in per cent on the ordinate and the corrected tonicity of the hypotonic mixture on the abscissa. Since the hypotonic mixtures contained 1.0 cc. of salt solution of known but different tonicities and 0.1 cc. of whole blood, the plasma contributed by the blood sample altered the final tonicity. Accordingly, the final tonicity of the hypotonic mixture was corrected assuming arbitrarily that the amount of plasma in each case was 55 per cent of the blood sample and that the plasma was osmotically equivalent to an 0.85 per cent solution of sodium chloride. Table 2 shows the osmotic-fragility values for 30 normal subjects with hemoglobin levels of 80 to 105 per cent, comprising 13 males and 17 females between the ages of seventeen and sixty-one. There was no significant difference between males and females.

*Observations made at the Massachusetts Institute of Technology.

TABLE 2. *Normal Osmotic-Fragility Values Expressed as Tonicity of Sodium Chloride.*

DEGREE OF HEMOLYSIS	1%	2.5%	5%	10%	50%	75%	95%
Maximum	0.49	0.47	0.46	0.45	0.41	0.40	0.35
Minimum	0.42	0.40	0.38	0.37	0.33	0.31	0.21
Average	0.45	0.43	0.42	0.41	0.38	0.36	0.30

Autoagglutinins (cold agglutinins)[27] and *hemolysins*[28] were tested for in the serum from clotted venous blood samples. The serums were diluted serially with physiologic salt solution and to each dilution was added an equal volume of 2 per cent suspension of Group O erythrocytes. As a source of complement for the hemolysis tests fresh human serum was then added in quantities equal to the patient's serum. These mixtures were observed for agglutination or hemolysis after being chilled for one hour at 0°C. and again after subsequent incubation at 37.5°C. for one hour.

HEMOGLOBINURIA

Observations were made on 40 patients with combined second-degree and third-degree thermal burns involving from 15 to 65 per cent of the body area. Eleven of these patients showed hemoglobinuria. The series includes 34 patients burned in the Cocoanut Grove disaster and 6 others. Detailed studies on 10 of the 11 patients showing hemoglobinuria (Cases 1–10) and on 4 patients showing no hemoglobinuria (Cases 11–14) are shown in Table 1. One patient with gross hemoglobinuria following a 65-per-cent burn sustained at Cocoanut Grove was omitted from the table because no determinations on the blood were made before death, which occurred in six hours. Gross hemoglobinuria was observed in 9 of 12 patients from Cocoanut Grove who showed combined second-degree and third-degree burns involving

45 to 65 per cent of the body area. Hemoglobinuria was not observed in the other 22 cases from the Cocoanut Grove including 12 cases showing severe burns involving 25 to 40 per cent of the body area. Since many cases of moderate or minimal hemoglobinuria may have escaped notice at the time of the Cocoanut Grove disaster, the incidence of hemoglobinuria is necessarily only a rough and minimum approximation. Hemoglobinuria of minimal degree was observed in 2 other patients (Cases 9 and 10) who received burns involving 30 and 20 per cent of the body area, respectively.

Hemoglobinemia, the occurrence of free hemoglobin in the plasma, was observed during the first twenty to thirty-six hours in Cases 1-8, with values ranging from 65 to 215 mg. of hemoglobin per 100 cc. of plasma. In Case 4, the plasma hemoglobin level decreased during sixty hours after the burn from 185 to 65 mg. per 100 cc., coincident with a decrease in hemoglobinuria. Spectroscopic examination of the plasma from this case revealed the characteristic absorption bands of oxyhemoglobin and, in addition, an increased absorption of light at approximately 620 millimicrons, which was not obliterated by the addition of sodium cyanide or hydrogen peroxide. The latter absorption band is characteristic of methemalbumin, as observed by Fairley[29] and confirmed by Fox.[30]

Observations on Urine and Kidney Function

In patients with gross hemoglobinuria the urine was scanty in amount for one or two days, varied in color from black to red to pale brown, and contained sediment varying from a trace to 5 per cent of the urine volume of brown or red material identified as precipitated hemoglobin and hemoglobin casts. The specific gravity was not materially elevated, varying from 1.010 to 1.022 in 5 cases tested. In observations on 8 patients with hemoglobinuria who had not received injections of sodium lactate, the urine was acid, the pH varying from 4.5 to 5.8, except in 1 case (Case 10) in which the pH was 7.0. Increased acidity of urine was observed, however, without hemoglobinuria in Case 13. Masses of hemosiderin were detected in the urine samples from 8 of 9 patients examined who had hemoglobinuria.

The red and brown pigments in the urine were identified by spectroscopic analysis as predominantly oxyhemoglobin mixed with traces of methemoglobin. There was no evidence in the urine of myohemoglobin,[31] observed in urine following crush injuries by Bywaters et al.[32] The amount of hemoglobin in urine samples varied from a trace in Cases 9 and 10 to a maximum observed value of 520 mg. of hemoglobin per 100 cc. of urine in Case 4. After rapid centrifugation of the latter specimen the concentration in the supernatant fluid was only 280 mg. per 100 cc., indicating that approximately half of the hemoglobin was precipitated from solution. The duration of hemoglobinuria could be only roughly estimated. The maximum excretion of hemoglobin in Cases 1-8 occurred during the first twelve or twenty-four hours, decreasing quite rapidly to a moderate amount or trace of hemoglobin within thirty-six to forty-eight hours. Since oliguria was marked in the first twenty-four hours, it was impossible to establish the time of onset of hemoglobinuria. It is probable, however, that hemoglobinemia occurred promptly after the burn.

Proteinuria other than hemoglobinuria occurred in the first twenty-four to forty-eight hours to a striking degree in Cases 2, 4, 10, 12 and 14 and to a moderate degree in Cases 3, 5, 6, 7, 8, 11 and 13. Thus, proteinuria of significant degree occurred with hemoglobinuria in Cases 2, 4 and 10 and without hemoglobinuria in Cases 12 and 14.

Oliguria occurred in the first twenty-four to forty-eight hours in most of the severely burned patients whether or not hemoglobinuria was present. There was, however, no case of complete anuria. Of 10 patients with hemoglobinuria, the nonprotein nitrogen of the blood was determined in 7 cases. Chronic azotemia of moderate severity occurred in spite of the re-establishment of adequate excretion of urine in 4 patients (Cases 5, 6, 7 and 10) who lived for periods of five to thirteen days after the burn. Transient azotemia occurred in the only surviving patient with hemoglobinuria (Case 8). Of the remaining 5 patients with hemoglobinuria, azotemia was observed in Case 4 in thirty-six hours, death occurring in seventy-nine hours; no observation or only an early one was made in Cases 1, 2, 3 and 9. Of 4 patients without hemoglobinuria, terminal azotemia occurred in Case 11, reversible azotemia occurred in Cases 13 and 14, and no azotemia was observed in Case 12 during a period of twenty-seven days following a severe burn involving 65 per cent of the body area. Azotemia in burned patients is discussed in detail by Taylor et al.[33]

No significant anemia occurred during the first twenty-four or forty-eight hours in the 14 burned patients, of whom 10 (Cases 1-10) showed hemoglobinuria. During this period, determinations of the hematocrit or of the concentration of hemoglobin in venous blood obviously had limited meaning because of the fluctuations in blood volume produced by the loss of blood plasma into the burned area or by the parenteral administration of plasma and other fluids. A delayed progressive anemia that developed at approximately the end of one week in Cases 6, 7, 8, 12 and 14 was observed by others.[34]

Histologic Examination of Kidneys

The kidneys were studied histologically in 9 patients.[35] In 3 patients (Cases 11, 12 and 13) who showed no hemoglobinuria there was no significant abnormality in the kidneys. In 6 patients (Cases 4, 5, 6, 7, 9 and 10) who showed hemoglobinuria the histology of the kidneys was consistent with that of hemoglobinuria, as evidenced by the finding of hemoglobin casts in the tubules in each case.

In general the histologic picture was as described below, with variations for particular patients, as indicated in Table 1. The casts in the tubules varied in number and appearance from typical hemoglobin casts to coarsely and finely granular, brownish or reddish casts. Some tubules also contained dense blue, hyaline material, occasionally polymorphonuclear leukocytes and mononuclear cells and, rarely, red cells. In some cases the epithelium of the tubules containing the hemoglobin casts showed evidence of degeneration and necrosis. The tubular epithelium was occasionally more granular than normal; in other cases there was evidence of regeneration of the epithelium of the tubules. In several cases the interstitial tissue showed areas of infiltration with lymphocytes, plasma cells and, rarely, eosinophils. In general the glomeruli and blood vessels were normal.

Changes in Red Cells

The osmotic fragility of the red cells was significantly increased above normal in 7 patients. Of these, 5 patients (Cases 1, 2, 4, 5 and 9) had hemoglobinuria and 2 patients (Cases 12 and 14) had no hemoglobinuria. No significant increase in osmotic fragility of the red cells was observed in 5 patients with hemoglobinuria (Cases 3, 6, 7, 8 and 10) and in 2 patients with no hemoglobinuria (Cases 11 and 13). It should be emphasized, however, that in 10 patients the earliest observation of the osmotic fragility was from seventeen to forty-four hours after the burn; the red cells in 6 of these 10 patients showed no significant elevation of the osmotic fragility. This interval was usually beyond the period of maximum hemoglobinuria and presumably, therefore, past the period of maximum blood destruction. The interval after the burn in which the initial observation was made of the osmotic fragility is shown in Figure 1. In 4 patients not from Cocoanut Grove, the osmotic fragility of erythrocytes was determined promptly, within a period of a half to three hours after the burn. The fragility was normal in only 1 of these patients (Case 11), whose burn involved 20 per cent of the body area. In the other 3 patients, the osmotic fragility was increased as follows: slightly in Case 12, burned 65 per cent; moderately in Case 14, burned 15 per cent; and extremely in Case 9, burned 30 per cent. In the last case, hemoglobinuria was observed at a time when the osmotic

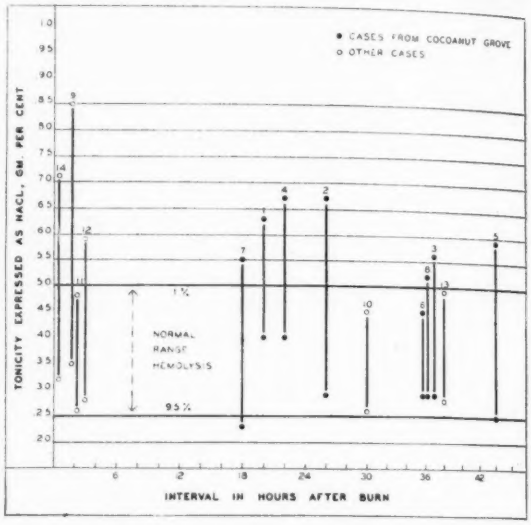

FIGURE 1. *Relation of the Interval after the Burn to the Osmotic Fragility of the Red Cells.*

The maximum range of osmotic fragility (from 1 to 95 per cent hemolysis) is shown for each of the 14 cases.

fragility test (Table 1 and Figure 2) indicated that 1 per cent of the patient's red cells were hemolyzed in isotonic (0.85 per cent) sodium chloride

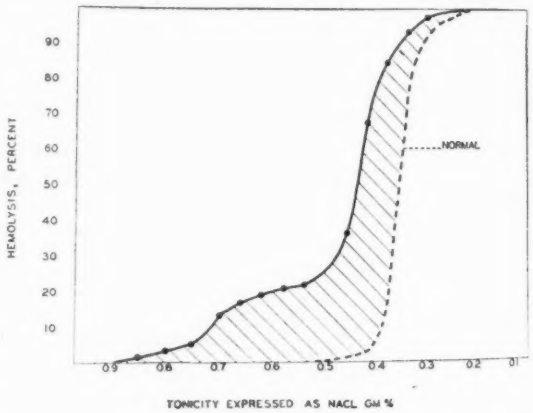

FIGURE 2. *Curve of the Osmotic Fragility of the Red Cells from Case 9.*

The cells were obtained two hours after a burn involving 30 per cent of the body, and three hours before the patient's death.

solution and thus, presumably, were susceptible to osmotic hemolysis in the patient's own isotonic blood plasma. The progressive disappearance and probable destruction of the red cells with abnormally increased osmotic fragility are shown for Cases 4 and 14 in Figures 3 and 4, respectively.

Blood smears from certain of the burned patients showed fragmentation, budding, spherocytes and microspherocytes of the red cells. Maximum fragmentation of red cells was seen only in the smears taken promptly after the burn, as in Case 14, shown in Figure 5. Deeply staining spherocytes, however, were detectable in significant numbers in Case 4 sixty hours after the burn, as shown in Figure 5. The spherocytes were observed to be significantly increased in number, being 3 per cent or above, in Cases 3, 4, 13 and 14, with simultaneous increases in osmotic fragility occurring in Cases 3, 4 and 14. In Case 13 the fragility was normal when determined thirty-eight hours after the burn, and accordingly the observation one hour after the burn of 3 per cent spherocytes in the blood smear constituted the only abnormality detected in the red cells. The disappearance of spherocytes from the blood smear coincident with the disappearance of red cells with increased osmotic fragility is shown in Figure 4.

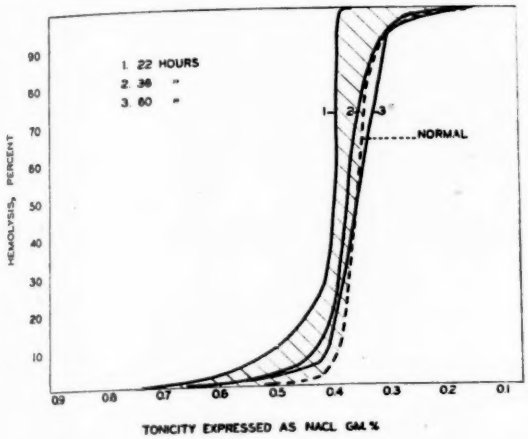

FIGURE 3. *Serial Curves of the Osmotic Fragility of the Red Cells from Case 4.*
This shows a progressive loss of abnormal cells up to sixty hours after the burn.

Since autoagglutinins or autohemolysins might have arisen from the thermal burn and might have influenced the red cells, these antibodies were sought for in samples of blood serum obtained from Cases 1-8 seventeen to thirty-seven hours after the burn. No "cold" or "warm" agglutinins or hemolysins were detected in these samples taken at a time when increased osmotic fragility was observed in Cases 1, 2, 4 and 5.

EXPERIMENTAL STUDIES ON HEATED BLOOD

The experimental studies on human blood heated in vitro and on dog's blood heated in vitro and injected into the same animal are summarized briefly below and will be reported fully elsewhere.

When samples of normal human defibrinated blood were heated in glass test tubes in a constant-temperature water bath to temperatures as high as 46°C. and the temperature was maintained constant for a period of one hour, no changes were observed in the erythrocytes. At temperatures of 47 to 50°C., abnormal changes in the red cells occurred depending on the duration of heating, which was extended to one hour as a maximum. Within a "critical zone" of temperatures (51 to 65°C.), abnormal changes always occurred even when blood samples were heated rapidly — in one and a half minutes — to a given temperature and immediately cooled to 37°C.

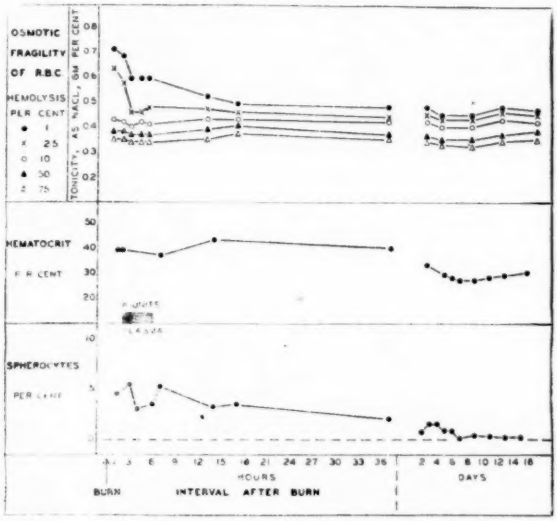

FIGURE 4. *Progressive Loss of Spherocytes and of Red Cells of Increased Osmotic Fragility in Case 14.*

These abnormal or "thermal" changes in the red cells occurred in a regular and reproducible manner. The first detectable alteration was the formation of increasing numbers of rounded, budlike projections or filaments, at first connected with and finally disconnected from the erythrocytes. Progressive increase in this process of fragmentation was associated with the appearance of spherocytes, microspherocytes mixed with occasional "ghosts" and many erythrocytic fragments varying in diameter from 1 to 2 millimicrons down to innumerable small particles, approximately the size of bacteria, showing active brownian movement in a wet preparation. Coincident with the appearance of spherocytes and microspherocytes in the smear, the osmotic fragility of the red cells increased above normal and progressed to a maximum range with the progressive increase in spherocytosis of the erythrocytes. When the osmotic fragility increased to the maximum range, some of the red cells were susceptible to hemolysis as ob-

served in the fragility test in isotonic (0.85 per cent) sodium chloride solution. Hemolysis of the red cells varied with the temperature and with the duration of heating. The amount of hemolysis was negligible when the osmotic fragility was normal, when it was increased only moderately, and in many cases when it was increased to the maximum range. Temperatures of 55°C. or above produced hemolysis that was progressive, ranging from 2 to 5 per cent of the red cells to complete hemolysis at 65°C. These thermal changes were inherent in the red cells themselves and did not depend on the medium in which they were suspended, whether plasma (heparinized), serum or isotonic salt solution, and were produced in vitro out of contact with the tissues. The serum from heated blood did not hemolyze or change normal red cells, and the serum from unheated blood did not reverse the changes in heated erythrocytes. When subjected to severe mechanical trauma for an hour in a test tube, blood that had previously been heated to 50°C., with a slight increase in osmotic fragility, showed no significant increase in susceptibility to hemolysis. However, after heating to 52, 55 and 58°C., respectively, the osmotic fragility and morphologic changes were maximal, and hemolysis from trauma increased progressively with the higher temperatures and was significantly greater than the hemolysis of blood heated to 50°C.

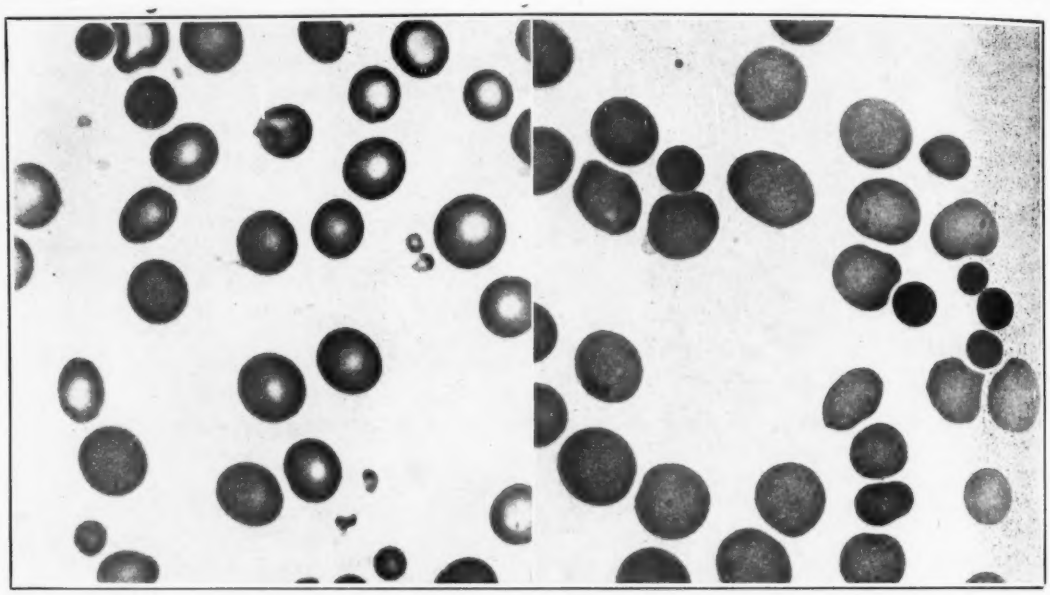

FIGURE 5. *Stained Blood Smears after Burns (× 1000).*

The preparation on the left was made half an hour after the burn in Case 14; that on the right, sixty hours after the burn in Case 4. Both show densely stained spherocytes, and that on the left, a certain number of fragmented forms.

The susceptibility to hemolysis of heated blood from dogs was observed in vitro by the osmotic-fragility test and in vivo by injection of the heated blood into the same animal. None of the animals were burned. Five healthy dogs weighing from 12 to 18 kg. were bled of one sixth to one fourth of their blood, followed by the intravenous injection of an equal volume of isotonic sodium chloride solution containing 40 cc. of molar sodium lactate. In observations on dogs 1, 2 and 3, about one fifth of each animal's blood volume was heated in vitro to approximately 53°C., producing maximum changes in morphology and in osmotic fragility, whether the red cells were heated in serum, washed and resuspended after heating in hypertonic (1.275 per cent) sodium chloride solution or washed and resuspended before heating in isotonic (0.85 per cent) sodium chloride solution. The heated suspension of red cells in each case was cooled to room temperature and injected into the same dog. Blood samples removed from these three animals immediately after injection showed an abnormal osmotic fragility comparable to the "mixed-population" fragility curves produced in vitro by mixing 20 to 30 per cent by volume of heated blood with unheated blood. The stained smear showed spherocytes immediately after injection. In the course of several hours after injection the spherocytes and abnormally fragile erythrocytes disappeared coincident with extreme hemoglobinemia and hemoglobinuria lasting for twenty-four to thirty-six hours. All three dogs recovered without reactions, without azotemia, and with the excretion of copious amounts of urine with a pH of

6.5 to 8.5. As a control observation in dog 4, one fifth of the blood volume was removed, defibrinated, heated to 50°C., and reinjected. This degree of heat did not change the osmotic fragility of the red cells. Following injections there was no change in morphology or osmotic fragility, no disappearance of the animal's red cells and no hemoglobinuria. In a second control observation in dog 5, one fourth of the blood volume was removed into sodium citrate as an anticoagulant and heated to 53.7°C., and only the plasma, obtained by centrifugation, was reinjected. The heating produced a maximum increase in the osmotic fragility and considerable hemolysis of the red cells. Injection of the deep-red plasma, which was free of cells and fibrin, did not alter the osmotic fragility of the dog's red cells and produced only slight and transient hemoglobinemia and hemoglobinuria.

Discussion

It is evident that hemoglobinuria as a complication of severe thermal burns results from the rapid destruction of red cells, producing hemoglobinemia with consequent excretion of free hemoglobin in the urine. Concerning the mechanism of hemolysis of red cells, no cold or warm agglutinins or hemolysins were found in samples of serum obtained from 4 patients at a time when their erythrocytes showed increased osmotic fragility. In 6 patients, the increased osmotic fragility occurred without or before sulfonamide therapy. In a patient (Case 9) whose osmotic fragility showed the greatest increase obtained in this series no chemicals were applied to the burn. There was no apparent clinical complication, such as pulmonary involvement, which was common to all cases either with hemoglobinuria or with increased osmotic fragility. All 14 patients received intravenous injections of large volumes of human plasma both with and without the development of hemoglobinuria or increased osmotic fragility. Other possible causes for destruction of erythrocytes may include intravascular thrombosis and possibly the formation of capillary emboli.[36]

By contrast, the positive evidence derived from the observations of the patients and from the experiments reported here in brief form supports the belief that the principal and immediate cause of the increased blood destruction in thermal burns is the heating of the circulating blood in the tissues adjacent to the burned area. This evidence can be summarized as follows: The red cells from certain of the cases reported here, examined promptly after the burn, revealed a mixed population of normal cells and of spherocytes of varying sizes. The erythrocytes exhibited varying degrees of increased osmotic fragility. In severe cases of burn, heating of the tissues probably occurs, since subcutaneous temperatures of from 51 to 65°C. have been produced and maintained for several minutes experimentally in anesthetized animals by scalding[19] and by igniting turpentine on the skin.[17] The heating of human blood in vitro within the critical zone of 51 to 65°C. produced irreversible and progressive fragmentation and formation of spherocytes, a progressive increase in the osmotic fragility in hypotonic salt solutions and hemolysis of some of the red cells in plasma, serum or isotonic salt solution. The effects produced by heat were inherent in the erythrocytes themselves and were not caused by demonstrable hemolytic agents or dependent on the presence of animal tissue, serum or plasma. The process of fragmentation apparently produced spherocytes and microspherocytes, possibly by removing from the erythrocyte a larger proportion of surface than of volume. If the usual osmotic properties of the surface and contents of the fragmented cells are retained, then from observations of Gänsslen,[37] Haden[38] and Castle and Daland,[39] spherocytes and microspherocytes will show an increase in osmotic fragility because their spheroidal shape permits less swelling before hemolysis occurs on reaching the spherical form, which is the form permitting no further increase in volume without increase in surface.

When the blood of dogs was heated sufficiently to cause increase in osmotic fragility and was then injected into the animal, presumably those red cells susceptible to hemolysis in vitro in isotonic sodium chloride solution were subject to osmotic hemolysis in vivo in the isotonic plasma of the animal. As for the less fragile erythrocytes susceptible to hemolysis only in hypotonic solutions, the mechanism of their destruction is probably analogous to that, for example, found in congenital hemolytic jaundice. As suggested by Ham and Castle,[40] cells that are not hemolyzed in isotonic salt solution or plasma may be slowly destroyed as a consequence of erythrostasis in the spleen and other organs. Thus, it has been demonstrated by the above authors and by Tsai et al.[41, 42] that the sterile incubation of normal human blood in vitro or the stagnation of animal blood in vivo leads to progressive increases in volume, spheroidicity and osmotic fragility such that eventually some of the cells are lyzed in isotonic salt solution, plasma or serum. The possible influence of mechanical trauma as a cause of hemolysis requires further study.

In contrast with the observations on hemoglobinuria in dogs, in which the urine was copious and neutral or alkaline in reaction, kidney complications developed in certain of the burned patients who showed hemoglobinuria. Most of the severely burned patients, during the first twenty-four hours, showed oliguria, acid urine and albumin-

uria, but this triad did not appear to be associated with the development of chronic azotemia. Of 3 patients without hemoglobinuria, terminal azotemia occurred in 1 and transient azotemia in 2. Similar observations have been reported by Lucido[48] and by Cope and Rhinelander.[7] When hemoglobinuria occurred with oliguria, however, chronic azotemia of moderate severity was observed in spite of re-establishment of adequate urine output in 4 of the 5 patients living more than five days. These were the only cases of chronic azotemia occurring in the 40 patients considered here whose burns involved from 15 to 65 per cent of the body area. This irreversible azotemia may represent a decrease in kidney function, but this cannot be established from the data available, especially in view of the large concentrations of nitrogen excreted in the urine, as reported by Taylor et al.[33] Also, the azotemia might have regressed if these patients had lived longer than five to thirteen days and had recovered from their extensive burns. From the clinical observations, the use of triple dye in treatment of the burned area was not a factor common to the occurrence of chronic azotemia, since it was not used in 1 patient (Case 10) who showed this condition. Also triple dye was used in 1 patient (Case 8) who showed reversible azotemia. Large amounts of hemoglobin can be excreted by the human or animal kidney without azotemia if the urine is adequate in volume and neutral or alkaline in reaction.[1, 2, 44] Hemoglobinuria[44, 45] and methemoglobinuria[46] in animals excreting acid urine, however, have produced oliguria and uremia. In the patients considered here with irreversible azotemia, histologic examination of the kidneys post mortem revealed hemoglobin casts in each case, but there was no extensive obstruction of tubules by these casts or advanced changes in interstitial tissue or in tubular epithelium. The histologic changes did not explain adequately the apparent inability of the kidney to clear the blood normally of its content of nonprotein nitrogen products. The occurrence of azotemia together with hemoglobinuria in these patients is similar only in part to kidney complications following intravascular hemolysis from blackwater fever or transfusion of incompatible blood.[44, 47] In these latter conditions the oliguria or anuria is usually protracted, resulting in higher degrees of azotemia, which may reverse completely with the re-establishment of diuresis. The mechanism of oliguria or anuria as related to the histology of the kidney in these conditions is a debated subject.[44, 48, 49] The immediate treatment of a severely burned patient, however, should probably include the administration of fluids and alkali in an attempt to establish prompt diuresis of neutral or alkaline urine.

In summary, it is probable that in thermal burns destruction of a considerable volume of erythrocytes may result directly from heating of blood at the site of the burn, depending on at least three major factors: the temperature attained by the blood, the duration of heating and the volume of blood subjected to these conditions. Accordingly, the thermal changes in blood may not correlate strictly with the area burned but may be anticipated in extensive third-degree burns. This concept possibly explains the high incidence of gross hemoglobinuria occurring in 9 out of 12 cases burned over a body area of 45 to 65 per cent in the Cocoanut Grove disaster. This fire may well have produced more intense and prolonged heating than did the source of burns in Cases 12 and 13, in which the patients were severely burned but showed no striking blood changes or hemoglobinuria.

The blood of burned patients, if examined early, may, as in this series, show alterations that vary from only slight spherocytosis of erythrocytes to advanced morphologic changes associated with an extreme increase in osmotic fragility involving 30 per cent of the patient's red cells, as indicated in Case 9 (Fig. 2). Correspondingly, blood destruction may be of a mild degree, as in Case 14 (Fig. 5), with no hemoglobinuria, or the rapid destruction of a considerable volume of red cells may be followed by hemoglobinemia, hemoglobinuria and possibly irreversible azotemia.

Summary

Gross hemoglobinuria was observed in 9 cases and minimal hemoglobinuria in 2 among 40 cases receiving combined second-degree and third-degree thermal burns involving 15 to 65 per cent of the body area. The maximum excretion of hemoglobin occurred during the first twelve to twenty-four hours, then decreased rapidly.

The urine samples from patients with gross hemoglobinuria were scanty in amount for one or two days, varied from black to red to light brown, and were acid (pH 4.5 to 5.8), and the urines contained hemoglobin in solution, in precipitated form and in casts. The red and brown pigments were identified spectroscopically as oxyhemoglobin mixed with traces of methemoglobin. There was no evidence of myohemoglobin.

The plasma or serum from 8 cases showed hemoglobinemia. Spectroscopically, oxyhemoglobin and methemalbumin were detected in the serum examined from 1 patient.

Chronic azotemia of moderate severity occurred in spite of the re-establishment of adequate excre-

tion of urine in 4 of 5 patients with hemoglobinuria who lived five days or longer. In 6 patients with hemoglobinuria examined post mortem, the histology of the kidneys was consistent with hemoglobinuria in each case. It is suggested that the immediate treatment of severely burned patients should attempt to establish diuresis of alkaline urine.

No significant anemia developed in the first twenty-four to forty-eight hours in the 14 burned patients, of whom 10 showed hemoglobinuria.

If blood is rapidly heated to a temperature of 51 to 65°C., changes occur in the red cells consisting of fragmentation and the formation of spherocytes and microspherocytes, with a striking increase in osmotic fragility and hemolysis of the erythrocytes.

In patients with severe or moderately severe thermal burns, the red cells examined promptly after the burn exhibited changes in morphology and osmotic fragility similar to those obtained by the injection into dogs of the animals' own erythrocytes heated in vitro to approximately 53°C.

The increased osmotic fragility of heated red cells apparently results from conversion of the normal biconcave erythrocytes to more nearly spherical forms by a process of progressive fragmentation. The mechanism by which heat causes fragmentation of red cells is not defined. It is possible that destruction of the red cells with increased osmotic fragility in vitro occurred through a mechanism of swelling and osmotic hemolysis in the isotonic plasma of the animal.

In thermal burns a significant number of erythrocytes may be destroyed by heat, probably depending on the temperature attained by the blood, the duration of heating and the volume of blood subjected to these conditions.

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THE RELATION BETWEEN THE FAMILY PHYSICIAN AND WAR INDUSTRY

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THE problem of absenteeism in war industry has received considerable mention during the past several months. It is with the solution of this problem as the goal that complete co-operation is being asked of civilian family physicians, and it is with such a thought in mind that this paper has been prepared. It is hoped to point out the seriousness of the condition and the factors involved in absenteeism, the job involved in preventive measures and the need for complete understanding and co-operation between the industrial physician and local attending physician, employees and the community as a whole.

It must be borne in mind that present-day conditions have brought into industry the very young worker, the relatively old worker and the female worker. These employees are inexperienced. In some cases they are physically below standard. Their environmental conditions are often poor. They have moved into localities near their places of employment, thus creating crowded and unsanitary conditions. All these factors furnish innumerable reasons for the present-day difficulties. They explain the frequency rate of accidents, the increase in rate of disabling diseases and the resulting absenteeism with its slowing of production of the supplies that the men at the front must have.

Industry itself has made sweeping progress in the handling of its medical problems. It has established complete medical and nursing services, hospitalization service and the means of education of the workers concerning hazard prevention and disease control, personal hygiene and sanitary methods, both at work and at home. In addition, it has established proper housing facilities, care for children of working mothers and ease in transportation to and from work. All these things are being done daily. What is the family physician doing to aid? What can he do to aid more?

Let us glance at the problem that confronts the industrial surgeon. He is far removed from the days when minor traumatic surgery was his chief concern. His job is one of preventive medicine, of medical supervision, sanitation and hazard control and of education of the employee.

The new employee is processed for his job. He must first undergo a strict and complete physical examination, often including visual acuity, pelvic examination in the case of women, serologic examination, urinalysis and x-ray studies of the chest. This pre-employment examination is not made for the purpose of disqualifying the prospective employee. It is done with one thought in mind: that of placing the applicant at the proper job, at the job that will not be detrimental to his health and at which he will be able to do the most work with the least possible disability. In this respect the family physician can be of great help.

Many people object to complete examination and to inquiries into their past medical histories. Many are afraid of the "blood tests." A word from their own doctors would save much time and lead to complete co-operation. There are occasions when a prospective employee has been asked to seek the advice of his family doctor because of an existing condition that has been discovered — hypertension, sugar in the urine, a positive serologic reaction or a pulmonary lesion that requires attention. This is done so that the employee will put himself under medical attention and so that his time lost from sickness will be at a minimum. Sadly enough, my own experiences have shown that instead of enlightening the patient, the family physician sometimes minimizes the condition. In other cases the family physician sends in a report reading, "I have examined this man and find him fit for work." He does this thinking that his statement will be of assistance in getting a job for his patient. This is entirely erroneous, because every bit of manpower is needed, and no person is refused employment if it is at all possible to hire him for some job, whether it be arduous, moderately heavy or light. On the other hand, valuable cooperation is given by the family physician who writes as follows: "I have examined this man and find him to have a hypertension (170/90). To my knowledge he has done work of a similar nature for the past ten years with no untoward effect. He is now under my care and will receive treatment periodically." With such a recommendation, the industrial physician feels safe in accepting this man for proper employment, and thus an attitude of friendly confidence is established.

In certain specialized fields, periodic examinations of employees are demanded. Here, too, the family physician can be of tremendous help in explaining to his patient that this is done merely as a protection, and that the employee is checked to see that an early difficulty is remedied so that he can be kept at his original position.

One of the greatest problems is that of examinations following illness. In most plants the work-

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er must be checked by the Medical Department before returning to work, and in most cases he is asked to present a written statement from his family physician concerning the nature of his illness. Here again my experience has been unfortunate. The notes from physicians have been worthless in the majority of cases. They simply state, "This man can now return to work." They do not include the diagnosis, nor do they indicate the severity of the complaint. They do not explain the number of visits or the possible necessity of subsequent visits. Industry is making every effort to check unnecessary absence and to lessen the extent of legitimate sickness absenteeism by keeping accurate statistical records and by analyzing and correcting the difficulties thus established. Certain plants are sending out visiting nurses mainly to help the patient during his period of recovery or to have him seek medical attention when he has not done so, in order that he can return to work at the earliest possible date. If the family physician would only acquaint himself with these facts, he would then understand the necessity for careful detailed explanations of his patient's absence.

Every effort is being made on the part of industry to return the worker to some job as soon as he is able to hold one after any illness. It would be wise for the family physician to acquaint himself with the type of work that the patient performs, so that he too can recommend return at an early date. In addition, it would be wise for him to know that there are always light jobs available for the worker who is weakened by some ailment, and to advise his patient to return to the Medical Department of his particular industry and be placed at such activity.

The increasing number of women in industry presents several problems. Many women with mild menstrual disorders find that the change of environment and the type of work to which they have subjected themselves increase their difficulties. All plants have the proper facilities for rest, nursing care and medication. For those who must lose one or two days regularly, work routines have been established so that they can make up the lost time. In severe cases, attention by the family physician is always suggested. Here his co-operation is of the utmost importance. He should make every effort to get his patient well as quickly as possible and should make sure that the job is not the causative factor. Those women who are suffering from menopausal vasomotor disturbances should be under the care of family physicians and receive appropriate therapy. Here, too, a detailed statement from the family physician will prevent improper placement of the worker. During pregnancy it is demanded that the worker receive ante-partum care and that she be released from her job at the thirty-second week of pregnancy. In all cases she must receive a statement from her physician to the effect that her work is not contraindicated. Nursing mothers, as a rule, should be refused employment.

The problem of proper care for children of mothers in war industry is a difficult one, and here the family physician can be of tremendous help in treating these children early and conscientiously.

Public-health authorities are waging a quiet and efficient battle against absenteeism. Recently in an industrial plant a group of several thousand men were prevailed on to stay at their jobs after they had begun a mass walkout because of the rumor of a contagious disease that was spreading among the workers. The public-health authority arranged a meeting with the management, the union officials and representatives from the workers. A program was established whereby corrective measures were instituted immediately and education of the workers as to their personal protection was begun. In this way, a tremendous man-hour loss was averted. At the Whittemore Ordnance Depot two similar experiences have occurred. In one case there was rumor of lead poisoning among the painters because of an erroneous statement. At the time an investigation of such a condition among both painters and battery men was being conducted. Conclusive laboratory evidence was discovered that no such condition existed. It was then possible to allay all fear among the workers. In the other case innumerable notes were received from family physicians stating that workers were suffering from carbon monoxide poisoning. This created considerable disturbance among hundreds of employees. The Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries which studied the matter, showed that the carbon monoxide content of the plant air was considerably below the 100 parts per million that was allowable. Had the family physician approached the Medical Department himself, this trouble would have been avoided.

The family physician should make every attempt to work with public-health authorities and with plant medical departments by assuring his patients of their efficacy. He should acquaint himself with the exact nature of his patients' jobs. His cooperation as concerns all the factors involved in eliminating absenteeism would make for complete understanding between the worker, the management, the plant medical department and the community as a whole, and in this way would be tremendously beneficial in helping toward greater production and complete advancement of the war effort.

CLINICAL NOTE

PNEUMOCOCCAL MENINGITIS: RECOVERY FOLLOWING TREATMENT WITH SULFADIAZINE AND SPECIFIC ANTISERUM

Report of a Case

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BEFORE chemotherapy became of common use, only in isolated cases was there recovery from pneumococcal meningitis. Prior to the use of sulfonamides, mortalities as high as 95 to 100 per cent were reported. The few scattered recoveries reported may have been due to specific antipneumococcus serum alone or may have been supplemented by various forms of drainage.[1] With the advent of the newer chemotherapeutic agents, the prognosis has been more promising.[2, 3] Some observers[4–6] have found that serum used in combination with the sulfonamides has made the outlook even better than when either is used alone. It is the purpose of this paper to report a case of pneumococcal meningitis with recovery and to give in detail the plan of treatment followed.

Case Report

S. G. A., a 12-year-old boy, entered the Pediatric Service of the Cambridge Hospital on August 24, 1942, in a semicomatose condition. Four days previously, an upper respiratory infection had developed, followed by earache on the right side. Approximately 20 hours prior to admission he had headache, stiff neck, nausea and intermittent vomiting. The family history and past history were irrelevant.

On admission the temperature was 105.5°F., the pulse 130, and the respirations 30. The blood pressure was 116/74. There was a marked bulging of the right tympanum, marked rigidity of the neck and positive Kernig and Brudzinski signs. Paracentesis of the right ear revealed purulent exudate. An x-ray film of the right mastoid showed no evidence of an acute inflammatory process. The spinal fluid was under a pressure of 250 mm. The fluid was cloudy, and a pure culture of Type 5 pneumococcus was isolated. There were 360 cells per cubic millimeter — 260 polymorphonuclear leukocytes and 100 lymphocytes. The protein was 192.5 mg. per 100 cc., the chlorides 643 mg., and the sugar 20 mg.

During the course of the illness four lumbar punctures were performed (Table 1). Because the patient appeared to improve clinically, these punctures were avoided as much as possible. An initial puncture was done to establish the diagnosis and to determine the etiologic agent. Owing to the presence of eye signs due to increased intracranial pressure, this procedure was repeated on the following day. Subsequent punctures were done to determine the progress of the case. As is evident from the table, the patient showed marked improvement in the 10-day period between the first and the last puncture.

Immediately after admission the patient was placed on a regimen of sulfadiazine, 45 gr. at once and 15 gr. every 4 hours thereafter. The initial dose was retained but subsequent doses were vomited. As a consequence, sodium sulfadiazine was given intravenously. Forty-five grains in 5 per cent glucose and saline solution was first administered, and this was followed 2 hours later by an intravenous injection of 30 gr. dissolved in 50 cc. of physiologic saline solution. The chemotherapeutic agent was then administered orally, in doses of 15 or 30 gr. every 4 to 6 hours. Concentrations of sulfadiazine in the blood were maintained in the vicinity of 20 mg. per 100 cc. On September 1, red cells began to appear in the urine, and medication was discontinued. The patient's general condition was considerably improved.

Since it was believed that combined drug-and-serum therapy would be of greater value than if either was used alone, the patient was simultaneously given Type 5 specific antipneumococcus serum, according to Table 2. Horse serum was first used, but this was changed to rabbit serum on noticing a mild chill following the second administration of horse serum. The administration of serum was continued until the quellung test on the serum had been positive on 3 successive days; a total of 930,000 units was given.

The patient responded promptly to therapy, and on the 3rd hospital day the temperature had fallen to normal. During the succeeding 9 days, however, it ranged from 100 to 102°F., becoming and remaining normal on and after the 12th hospital day.

Table 1. *Spinal-Fluid Findings.*

Date	Initial Pressure	Character	Cell Count			Sugar	Protein	Chloride	Culture
			total	lymphocytes	polymorphonuclears				
	mm. H_2O		*per cu. mm.*	*per cu. mm.*	*per cu. mm.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	
8-24	250	Moderately cloudy	360	100	260	20	193	643	Type 5 pneumococcus
8-25	350	Moderately cloudy	310	120	190	27	103	650	Type 5 pneumococcus
8-27	110	Cloudy	–	–	–	–	–	–	–
9-3	126	Clear	27	18	9	45	35	680	No growth

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Comment

After the diagnosis of Type 5 pneumococcus meningitis was established by culturing the organisms from the spinal fluid, it was believed that the case warranted the use of both sulfadiazine and specific antipneumococcus serum. As a result, the patient was given both forms of medication simultaneously. Because of his inability to retain the chemotherapeutic agent, the sodium salt of sulfadiazine was employed intravenously. Seventy-five grains of sodium sulfadiazine was thus used. This was followed by oral administration of the drug. At the same time specific antipneumococcus serum was given. The first ten doses were administered intravenously, and the remainder intramuscularly. During the first 24 hours, the patient received 670,000 units, consisting of 30,000 units from horse serum and 640,000 units from rabbit serum. A change to rabbit serum was made because of the apparent — though mild — chill reaction following the second dose of horse serum, because the prospect of large and repeated doses of serum would be required, and because it is thought by some that the rabbit-serum antibody, being a smaller molecule than the horse-serum antibody, may have a better penetrating action than the latter. Serum therapy was continued during the next 4 days by less frequent injections, mostly intramuscularly. A total of 930,000 units of Type 5 antipneumococcus serum was administered throughout the illness.

Table 2. *Dosage of Antipneumococcus Serum.*

Date	Time	Dose of Horse Serum		Dose of Rabbit Serum		Route	Reaction	Remarks
		cc.	*units*	*cc.*	*units*			
8-24	6:00 p.m.							Horse serum eye-sensitivity test, negative
	6:30 p.m.	2	6,000			Intravenously	None	
	8:30 p.m.	8	24,000			Intravenously	Slight chill	
	11:45 p.m.							Rabbit serum eye-sensitivity test, negative
8-25	12:15 a.m.			2	8,000	Intravenously	None	
	1:30 a.m.			8	32,000	Intravenously	None	
	3:00 a.m.			10	40,000	Intravenously	None	
	4:30 a.m.			25	100,000	Intravenously	None	
	6:30 a.m.			15	60,000	Intravenously	None	
	11:00 a.m.			25	100,000	Intravenously	None	
	7:00 p.m.			25	100,000	Intravenously	None	
8-26	11:00 a.m.			25	100,000	Intravenously	None	
				25	100,000	Intramuscularly	None	Quellung test on serum, negative
8-27	11:00 a.m.			25	100,000	Intramuscularly	None	Quellung test on serum, positive
8-28	11:00 a.m.			25	100,000	Intramuscularly	None	Quellung test on serum, positive
8-29	11:00 a.m.			15	60,000	Intramuscularly	None	Quellung test on serum, positive

The tympanum of the right ear was incised on the day of admission and a purulent discharge was noticed. Culture from this exudate failed to reveal any pneumococcus organisms. This was, however, apparently not a case of primary meningitis but one of meningitis secondary to otitis media. Frequent x-ray films of the right mastoid region were taken on the theory that if there was any evidence of an inflammatory condition, mastoidectomy with a view to wide drainage ought to be done immediately. The films showed no such inflammation at any time.

Summary

A proved case of Type 5 pneumococcus meningitis with recovery is reported, with the plan of treatment outlined in detail. Both a chemotherapeutic agent and the specific antipneumococcus serum were employed. At no time did it appear advisable to institute mastoid surgery.

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MEDICAL PROGRESS

THE ANEMIAS OF PREGNANCY

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IN 1842, Channing[1] described a condition of severe anemia that occurred in the course of, and apparently as the result of, pregnancy. In 1919, Sir William Osler,[2] in a paper entitled "The Severe Anemia of Pregnancy," again drew attention to this condition and suggested that it had not received the study that it deserved. It is only during the last few years that any serious attempt has been made to classify the various anemias associated with pregnancy and to discover the factors that are responsible for the changes in the mechanics of blood manufacture and maintenance during this period. Despite the fact that a woman with anemia is inadequately fitted to the trials of labor, routine red-cell counts and hemoglobin determinations are too rarely done, either at antenatal clinics or in private practice.

Although pregnancy is a physiologic and normal condition that in a normal woman, provided an adequate and reasonable diet is taken, has no effect on the general health and no pathologic effect on the hematopoietic system, the requirements of the growing fetus, the alteration in maternal metabolism and the ordeal of labor, with its consequent blood loss, frequently cause anemia. Adair, Dieckmann and Grant,[3] at the Chicago Lying-in Hospital, in a survey of 7835 patients, found that 63 per cent were anemic. Other American investigators — Lyon,[4] Galloway[5] and Moore[6] — with various methods of estimation, examined groups ranging from 100 to 1176 in number, and gave figures varying from 19 to 81 per cent of patients with less than 70 per cent hemoglobin. Various investigators have found this same condition in other countries.

Reid and Mackintosh[7] investigated a group of 1108 pregnant women and found that 45.9 per cent gave a hemoglobin reading of 86 per cent or over, 43.9 per cent showed a reading between 70 and 84 per cent, and 10.2 per cent gave a reading of below 70 per cent. When the women were divided into two groups according to the family income, it was found that the incidence of anemia was considerably higher in the low-income group. The investigations of Bland, Goldstein and First[8] showed the same thing. Multiparity in good financial circumstances does not appear to have much influence, except in women with five or more pregnancies, in which group the percentage with a hemoglobin reading below 70 per cent is three times as great as in those with fewer pregnancies. Age, work outside the home and abnormality in pregnancy have no demonstrable influence on the degree of anemia.

The anemias that are encountered in pregnancy fall into the following simple classification:

A. Coexisting with, but unrelated to, pregnancy.
   1. Pernicious anemia, chronic chlorosis and leukemia.
   2. Anemias due to pre-existing chronic disease (namely, chronic nephritis).

B. Anemias due to complications of pregnancy (namely, pyelonephritis, sepsis and bleeding).

C. Anemias due to pregnancy.
   1. Physiologic anemia of pregnancy.
   2. Hypochromic anemia of pregnancy.
   3. Macrocytic anemia of pregnancy.

In this paper it is proposed to discuss only the anemias directly due to pregnancy.

PHYSIOLOGIC ANEMIA

The gravid state is commonly associated with important and well-marked changes in the circulatory mechanism. One of the most important physiologic alterations is an increase of blood volume. Dieckmann and Wegner[9] determined the blood volume by the intravenous injection of vital red, and calculated the relative proportion of plasma and red cells by means of the hematocrit. These determinations were made on the same patients at intervals throughout pregnancy. The authors found an increase in plasma volume, total red cells and total hemoglobin, but since the increase in plasma volume is greater than the increase in the other two, although the actual number of circulating red cells and amount of hemoglobin are increased, the blood is more dilute. By ordinary methods of estimation there is, therefore, an apparent anemia affecting both the red cells and the hemoglobin. These are both proportionately reduced so that the color index remains at unity. By this means one can quite easily differentiate

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this condition from the iron-deficiency anemias, in which the color index is below 1.0.

Adamson and Smith[10] in a study of 116 normal pregnant women found that during the second trimester there was a gradual drop in hemoglobin from an average of 76 to 68 per cent, and a drop in the red-cell count to 4,000,000. During the third trimester the hemoglobin continued at an average of 67 per cent, the red cells remaining about the same. In the two weeks following delivery, however, the blood rapidly returned to normal. Only 2 per cent of the patients continued through pregnancy without some drop in hemoglobin. Kühnel[11] in a carefully controlled study concluded that there is a gradual drop in the hemoglobin, cell volume and red-cell count until the sixteenth to the thirty-second week. This low level is maintained until about the thirtieth to the thirty-second week, when these substances begin to increase, but at thirty-four to thirty-six weeks a level is reached that is still lower than the initial one. Dieckmann and Wegner's[12] investigations showed an average decrease in the hemoglobin concentration amounting to 15 per cent at twenty-five to thirty-five weeks. From then on until term the hemoglobin increased and in many cases reached a normal level. At term the blood volume showed an average increase of 23 per cent, the plasma one of 25 per cent, and the total red-cell count one of 20 per cent, thus accounting for the decrease in hemoglobin concentration, cell volume and red-cell count seen in normal pregnancy. These authors demonstrated for the first time that although there are marked variations of all the indexes, especially of the color index, in the same patient, the average for each remains close to 1.0. The cell volume is slightly increased between the twenty-sixth and thirty-fifth weeks, when the physiologic anemia is most marked. The corpuscular hemoglobin is also slightly increased, both in amount and in percentage, but is normal at term. The means for the hemoglobin concentration in pregnancy are 11.56 gm. per 100 cc. of blood, for the cell volume 37.31 per cent, and for the red count 3,770,000. From these figures Dieckmann and Wegner conclude that the minimal standards for normal pregnancy are 10 gm. of hemoglobin, a hematocrit of 33 per cent and 3,360,000 red cells. Wintrobe[13] in a careful study has shown that the lower limit of normal for the hemoglobin concentration in nonpregnant women is 13 gm. per 100 cc.

In the course of investigating blood volumes in many types of cases, Keith, Rowntree and Geraghty[14] observed a post-partum decrease in total blood volume of approximately 1000 cc. They considered that only about 300 cc. of this could be accounted for in blood lost at the time of delivery. This observation also serves to explain, on the basis of dilution, the low hemoglobin before delivery and the relatively high estimations observed after it.

The smear shows no abnormality. There is no evidence of pathologic destruction of red cells, and nothing to suggest abnormal regeneration, such as nucleated red cells, polychromatophilia or reticulocytosis. The rise in blood values that occurs just after confinement cannot, therefore, be due to new blood formation.

This type of anemia is quite common, and does no apparent harm to mother or child. It entirely disappears during the first two post-partum weeks and, being physiologic, requires no treatment.

Hypochromic Anemia

Hypochromic, secondary or, as it is sometimes called, microcytic anemia of pregnancy occurs in women who have a subnormal hemoglobin in early pregnancy, and when the physiologic anemia develops, the drop in hemoglobin is so great that symptoms and signs of anemia occur; these may clear up or persist after delivery. Hypochromic anemia is extremely widespread, having been reported from all European countries, India and the Far East. It may occur with pregnancy at any age (Bland, Goldstein and First,[8] Strauss and Castle[15] and Mackay[16]).

In 1929, Lyon[4] showed that over 30 per cent of pregnant women of the hospital class manifest some degree of hypochromic anemia, and Adair et al.[3] found that 23 per cent of 1176 patients at the Chicago Lying-in Hospital had a hemoglobin of less than 10 gm. per 100 cc. Adair states that in Bengal nearly all the anemias of pregnancy are of the secondary type, and that the average hemoglobin of a native woman is about 50 per cent.[36]

Although in a normal and robust woman the circulatory and hematopoietic adjustments in physiologic anemia as outlined above are sufficient to compensate for the demands of pregnancy, it is obvious that a woman who ordinarily maintains her full complement only with difficulty may, by reason of the pregnancy, easily become anemic. The fetus requires large quantities of maternal iron; the appetite, especially for iron-containing foods, may be capricious; the gastric function may be temporarily deranged; and any anemia that already exists is liable to exaggeration.

The mother has to supply the fetus, not only with sufficient iron to begin life, but also with sufficient store in the liver to carry it while on a diet consisting chiefly of milk, which is poor in

this mineral. The demand on the mother by the fetus for essentials of hematopoiesis has been likened to a chronic blood loss from other causes and represents a drain on the mother, especially during the latter part of pregnancy. The iron stores for the fetus must come either from the iron stores of the mother or from her food, according to Heath and Patek.[17] They state that if 10 per cent reduction in hemoglobin results from hydremia, which may account for hemoglobin levels of about 70 per cent, a further reduction of 20 per cent, owing to demands of the fetus for iron, would reduce the hemoglobin to 50 per cent, assuming no stores or food source in the mother. There are said to be 500 mg. of iron in the average fetus (Sodeman[18]). Since the fetus requires more and more iron as it becomes larger, it is obvious that hypochromic anemia would tend to manifest itself or become definitely severe during the last three months of pregnancy. It is thus easy to see that this mineral drain by a ruthless intrauterine parasite may readily bring about an acute anemic breakdown in the mother, whose own reserves are thereby exhausted.

The maternal iron reserves are dependent on two factors, intake and absorption. If the intake is small, the maternal store may easily become depleted, and it is well known that a patient with the capricious appetite found commonly in pregnancy often does not relish the iron-containing foods. There is a widespread belief that meat is bad for pregnant women, and many women on their doctors' orders to take a diet throughout pregnancy that is deficient in essential factors, especially iron.

Impaired gastric secretion, leading to defective utilization of iron, appears to be a contributory factor. Strauss and Castle[19] and Davies and Shelly[20] found that patients with hypochlorhydria or achlorhydria have a severer degree of anemia than do those with normal acid secretion. The anemia is typically hypochromic and microcytic. The hemoglobin is below 70 per cent and is commonly in the region of 50 per cent when advice is sought. The red cells usually number from 3,500,000 to 4,000,000 per cubic millimeter. The mean corpuscular volume, the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration are all low. The leukocytes and platelets are unaffected. The red cells have a low mean diameter.

Strauss and Castle[19] carefully followed during pregnancy 30 consecutive patients with uncomplicated hypochromic anemia whose hemoglobin and red-cell concentrations were less than half of normal. The chief presenting symptoms, appearing usually at about midpregnancy or later, were a lack of sense of well-being and an excessive sense of fatigability. The average age of these patients was thirty-two years, and the average number of previous deliveries between five and six. In the severer cases pallor was observed. Atrophy of the papillae of the tongue was common. Brittle and suggestively spoon-shaped fingernails were seen in a few patients. Splenomegaly, disappearing with adequate treatment of the anemia, was observed in 4 cases. Achlorhydria persisting until after delivery was found in 17, hypochlorhydria in 10, and normal acidity of the gastric contents in only 2 of the 29 patients examined. The red-cell count of these women ranged from 2,120,000 to 4,830,000, and the hemoglobin from 25 to 44 per cent.

Patients do not die of this type of anemia. No knowledge of the post-mortem findings is therefore available, nor have biopsy examinations of the bone marrow been made.

Except in severe cases, the ultimate prognosis is good and labor is uneventful if there is no undue post-partum hemorrhage. The fetus itself is born with a normal red-cell count. In severe cases there may be great prostration with dyspnea and edema. Albuminuria may occur. The patients who are efficiently treated may go to term without difficulty and recover completely during the puerperium after a few weeks of iron treatment.

A regular rest period during the day should be insisted on. A full diet, including meat and fresh green vegetables, is important, although the appetite may require stimulation. The essential treatment is the taking of iron. There are many effective preparations available, but ferrous sulfate, 0.8 gm. daily, ferric ammonium citrate, 6 gm. daily, and Blaud's pills, 4 gm. daily, are time-tested agents. Liver preparations have little or no effect on this form of anemia. Constipation should be corrected, provided treatment with iron does not eliminate this fault.

When hypochromic anemia is complicated by infection, a low basal metabolic rate, nitrogen retention or severe damage to vital organs, the effect of iron therapy may be disappointing, but the attempt should nevertheless be made.

Macrocytic Anemia

The macrocytic anemias of pregnancy constitute a much more dangerous complication than those of the iron-deficiency group, but are uncommon in this country. In the past the mortality rate was quite high, and it was probably this type that drew the attention of Channing in 1842 and Osler in 1919. With the development of modern methods and modern classifications, the macrocytic form of

anemia can now be clearly separated from the hypochromic anemia of pregnancy, and it is probable that the next few years will enable a proper estimate to be made of the true incidence of the former disease. Bardy,[21] in 1924, reviewed 68 cases collected from the literature of Europe and America during a period of thirty-eight years. Esch,[22] in 1921, was able to find only 23 cases in the German literature.

This anemia is often referred to as pernicious-like or pseudopernicious anemia of pregnancy to differentiate it from true pernicious anemia. Indeed, the blood smear shows all the characteristics of pernicious anemia. Occasionally the differential diagnosis is difficult. Macrocytic anemia occurs in younger patients than does pernicious anemia, and usually develops during the last three months of gestation, but is often not recognized until shortly after delivery. Usually the pregnancy continues in a normal manner, with the patient becoming gradually paler or exhibiting a slightly jaundiced appearance, until the sixth or eighth month, when fainting, collapse, edema, albuminuria or excessive paleness may occur quite suddenly. In severe cases, edema and albuminuria give a clinical picture suggestive of nephritis, whereas coma may suggest toxemia. Syncopal attacks and retinal hemorrhage are not uncommon, but spinal-cord changes and glossitis do not arise. Rarely after the stress and shock of labor and delivery, the enfeebled patient suddenly collapses and becomes moribund. Premature labor is common, and the outlook for the infant is poor. Fever without demonstrable infection is not unusual, and when it occurs post partum may suggest puerperal sepsis. It disappears with anemia therapy. Retinal hemorrhages have been described by Hoskin and Ceiriog-Cadle[23] and Cornell.[24] Gastrointestinal disturbances are of common occurrence.

Strauss and Castle[19] found in a series of cases, that the red-cell count varied from 1,050,000 to 2,500,000 and the hemoglobin from 20 to 50 per cent (Sahli), resulting in a color index above 1.0. The red cells showed moderate variation in size and shape, with microcytes, occasional poikilocytes, oval macrocytes and rare megaloblasts. The leukocytes and platelets were either normal or slightly decreased. The mean corpuscular volume ranged from 105 to 130 cubic microns.

There is considerable disagreement concerning the question of recurrence in future pregnancies. Allan[25] does not consider that there is an association between the two. Reist,[26] on the other hand, says that the anemia, once established, tends to recur in subsequent pregnancies at an earlier date and to grow severer with each successive pregnancy. This has also been stated by Vermelin and Vigneul[27] and Murdock.[28]

The prognosis of both mother and child has been greatly improved in recent years owing to the development of blood transfusion and liver therapy. In untreated cases the mortality rate is high, being from 30 to 75 per cent for the mother and even higher for the infant. Cases that are treated early and energetically can safely be allowed to go to term. MacLeod and Wilson[29] describe a patient who was quite symptomless and uncomplaining until she suddenly collapsed and became moribund, and there are many other similar cases in the literature. Recovery is considerably retarded by sepsis. Most patients begin to recover with the birth of the child, and many have recovered spontaneously without treatment, once delivery is over. Soon after delivery there is usually a marked increase in reticulocytes.

The earlier writers called the macrocytic anemia of pregnancy "hemolytic anemia of pregnancy," but this term should be discarded because hemolysis is not a feature of the disease and is not caused by a hemolytic or toxic agent. Strauss and Castle[19] have shown that the hematopoietic principle is probably deficient because of a temporary derangement of gastric secretion due to the pregnancy. The response of liver therapy is exactly the same as that found in true pernicious anemia, so that it is assumed that the anemia is due to the lack of hematopoietic principle. A deficiency in absorption may also be a factor.

Treatment consists in the administration of large doses of liver extract parenterally, and the response is as dramatic as in true pernicious anemia. Generally the use of liver preparations can be discontinued a few weeks after delivery, but it is well to maintain patients under observation, since it is possible for them subsequently to develop true pernicious anemia. If labor is not imminent, there will usually be sufficient recovery to allow of a normal labor without excessive danger or distress to the mother. Since there is frequently a partial deficiency of iron, it is well in addition to use iron in moderate dosage.

Patients who are desperately anemic or in whom infection is present and labor imminent should receive a blood transfusion, which may have to be repeated. Kersley and Mitchell[30] stress the value of transfusion in preventing obstetric shock in anemic patients. Matching of the blood for transfusion may be difficult owing to the factor of autoagglutination, which is sometimes present to a marked degree. Stewart and Harvey[31] state that there is no difficulty if the test is performed at a temperature of 37°C.

In recent years, with the increasing popularity of blood transfusion as a therapeutic procedure, occasional cases are encountered of hemolytic reactions following the use of blood of the same group as that of the patient. These have been attributed to the presence of irregular isoantibodies in the patient's serum, but in all cases such antibodies were not demonstrable by cross-matching tests. New information on this point was obtained in 1940 when Landsteiner and Wiener[32] detected a new factor in human blood (Rh) unrelated to agglutinogens A and B, and shortly thereafter Wiener and Peters[33] observed 3 cases of hemolytic reactions, 1 fatal, in which isoantibodies for this factor were present in the patients' serums. There were patients who had received previous transfusions, the anti-Rh isoantibodies being most likely the result of isoimmunization. Furthermore, it was found that transfusion accidents can occur at an initial transfusion owing to isoimmunization in pregnancy, the fetus in utero supplying the antigen (Wiener and Peters,[33] Levine and Stetson[34] and Levine, Katzin and Burnham[35]). Some of these accidents had previously not been recognized as related to the transfusion but were believed to be merely pregnancy complications. Apparently the great majority of the reactions in repeated transfusions and in pregnancy cases are due to the Rh factor.

The condition is usually easily prevented by the optimal nutrition during pregnancy. The diet should contain adequate amounts of meat, eggs and whole-grain cereals.

* * *

During pregnancy, a mild type of anemia, physiologic in origin, is usually present. It does no apparent harm to mother or child and requires no treatment.

In this country, hypochromic anemia of a mild degree during pregnancy is not uncommon, and although seldom dangerous to life, is nevertheless responsible for minor ailments and ill health in both mother and child. It can readily be cured by iron therapy and a generous diet.

Occasionally anemia of a severe and dangerous degree develops during and as a result of pregnancy. This demands detailed hematologic investigation, accurate diagnosis and prompt treatment.

Determinations of the hemoglobin level and of the red-cell count at about the sixth month of pregnancy should form an essential part of antenatal supervision. Subsequent hematologic studies and therapeutic measures can then be carried out when abnormality is found.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
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CASE 29441

PRESENTATION OF CASE

A thirty-eight-year-old man entered the hospital because of recurrent dyspnea of five years' duration.

Twenty-four years before entry, at the age of fourteen, the patient first noticed swelling in his neck. He was treated for several years by iodine and x-ray, without relief. At the age of twenty-one the right lobe of the thyroid gland was removed at an outside hospital. Following the operation he was told that he did not have a "toxic gland." The swelling and dysphagia, however, persisted. Five years later, at twenty-six years of age, the basal metabolic rate was said to have been normal and x-ray studies were said to have shown displacement of the trachea. He apparently received x-ray treatment and then was again operated on. There was a great deal of hemorrhage during the operation. Following the operation there was a persistent lump on the left side of the neck. Five years before entry he had a two-minute episode of dyspnea, during which he felt "strangled" and could not breathe in. Ten days before admission he had a similar episode while brushing his teeth. From both of these he recovered spontaneously. There had been no dysphagia, tremor or sweating. He had averaged 1 gr. of thyroid daily since the last operation.

An appendectomy had been performed two years before admission. One year later he had an attack of pain in the right flank and diarrhea.

Physical examination showed two transverse operative scars on the neck. Old x-ray changes were present in the skin over the suprasternal region, consisting of atrophy and multiple telangiectases. The left lobe of the thyroid gland was firm and measured 4 by 6 cm.; the isthmus was also palpable and firm. Examination was otherwise normal.

The blood pressure was 140 systolic, 90 diastolic. The temperature was 98.6°F, the pulse 70, and the respirations 22.

The blood showed a hemoglobin of 14.9 gm. and a white-cell count of 9100. The urine examination was negative. The basal metabolic rate was +2 per cent.

An x-ray film of the chest showed a soft-tissue mass in the left side of the neck that displaced the trachea to the right and the esophagus posteriorly; no diverticulum was seen. The heart, lungs, aorta and diaphragm were normal.

On the fourth day a left thyroidectomy was performed under intratracheal nitrous oxide, oxygen and ether anesthesia. Considerable difficulty was encountered during the operation. The tissues seemed to be extremely vascular and densely adherent, without any planes of section. A lobulated mass, which in the upper portion measured 7 by 4 by 4 cm. and in the lower portion 5 by 4 by 4 cm., was finally removed. During the procedure the patient was carried under deep ether anesthesia, and at one time respirations had to be augmented by positive pressure to the bag, which was in the closed circuit. He received intravenous fluids and 500 cc. of whole blood. At the end of the operation his condition was fair. The systolic blood pressure was 60, and the pulse 120. On removal of the intratracheal tube, the airways remained clear. The blood pressure slowly rose with the patient in the shock position and continued intravenous fluids.

During the night of operation the systolic blood pressure was around 100, and the pulse 90 to 100. There was no evidence of hematoma in the neck, and only the usual moderate staining of the dressing. The patient remained in coma and twenty hours postoperatively had a right facial weakness. The pupils were moderately dilated and fixed. The corneal reflexes were absent. The blood pressure was 130 systolic, 80 diastolic. The pulse, which had been 80, increased to 100 but was regular. The temperature rose to 102°F. Twenty-four hours after operation he had an episode of projectile vomiting, following which the respirations became less frequent and more shallow. Although the air passages seemed clear, respirations finally ceased.

DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: This seems to be a double header. I have to guess what kind of thyroid disease this patient had and also why he died.

Let us review a number of points that should be discussed. I am going to assume that the swelling of his neck at the age of fourteen was an enlarged thyroid gland. I have no adequate physical examination to permit me to make that statement flatly, but they say later on that they took out his thyroid, so I shall assume that it was thyroid. I might point out that there is no evidence in the story that the goiter was ever toxic. He was

*On leave of absence.

treated, however, early in the course of the disease with iodine and x-ray without relief. That is not surprising because it does not sound like the kind of goiter that I should expect to be relieved by either of those procedures. The only goiters that I know of that are benefited by x-ray are toxic goiters, certain malignant goiters or that form of chronic thyroiditis known as lymphadenoid goiter or Hashimoto's struma.

I am interested in the fact that the patient had a great deal of hemorrhage from the second operation. Does that in any way have a bearing on the postoperative death at thirty-eight? I do not suppose it has, but it just passed through my mind that in women, sometimes after severe post-partum hemorrhage, the pituitary gland becomes infarcted and they develop Simmonds's disease later. I do not believe that anything of this sort occurred in this case, but I throw it out as something that might pass through one's mind in considering the case.

Even after the second operation the patient had a persistent lump in the left side of his neck. The episodes of dyspnea interest me. The caption at the top says that he came in for recurrent dyspnea of five years' duration. He had two attacks,—one at the beginning and the other at the end of this period,—which seems to me not exactly recurrent dyspnea of five years' duration. He did have two peculiar attacks that were characterized by dyspnea and a sense of strangling. That sounds to me like stridor of some sort rather than cardiac dyspnea or even asthma, although I suppose it could be.

He had received thyroid since his second operation. Why, I do not know. Nothing is stated to indicate that he was suffering from hypothyroidism. He had a good deal of the thyroid gland taken out, but we have no evidence on which to base a diagnosis of hypothyroidism.

We have to figure out what kind of goiter he had, and why he died. There are any quantity of things missing from this record that would be of diagnostic help to me. Perhaps to my later sorrow, I am going to throw out the pain in the right flank and the diarrhea as not bearing on the major issue.

This is a rather sketchy physical examination. There is no record of a Chvostek or Trousseau sign. I do know that when anyone gets a history of stridor after two thyroidectomies, one certainly would want to look at the vocal cords; but there is no mention of that either. I should like a better examination of the neck. They say that the thyroid gland was firm and that they felt the isthmus. I would want to know about the consistence and the surface, whether it was adherent to anything, or if there were any palpable lymph nodes. Since they state that it was "otherwise negative," I shall assume that no lymph nodes were felt.

The x-ray examination disclosed a goiter in his neck, but not in his chest, which pushed the trachea to the right and the esophagus backward. It would be disconcerting if this turned out to be not a goiter at all but some other cervical tumor. I should also like to know whether it went up or down when he swallowed. Maybe they did not try that.

DR. BENJAMIN CASTLEMAN: You have everything that is in the record, Dr. Means. I suppose the scantiness of the record is due to the fact that the patient was in the private pavilion of the hospital.

DR. MEANS: We know that the trachea and esophagus were compressed. Therefore, they did a thyroidectomy. That is right and proper. What are the indications for thyroidectomy in general? Thyrotoxicosis, under certain circumstances but not always, the production of pressure, and the suspicion of malignancy or the knowledge that it is malignant. I suspect they took out this goiter because of pressure. They may have thought it was malignant, or even that it was a constricting thyroiditis.

What kind of goiter did they take out? I do not believe that the patient had hyperplastic or simple colloid goiter. The general course and the chronicity of this disease are consistent with an old, nodular, partly adenomatous, partly cystic goiter. I cannot say that it is not some form of chronic thyroiditis, like Riedel's struma. On the other hand, I cannot say that it is, because we do not have the information. It could be a lymphadenoid goiter, but I do not believe that it was. He may have had an adenomatous or a cystadenomatous goiter for a great many years and had a malignant change in it. It would be impossible for me to say. Sometimes even the pathologist has difficulty in determining whether a goiter is malignant.

The next thing that intrigues me is the difficulty that the surgeons had at the time of operation. From the description it was difficult to remove this goiter. In fact the patient did not survive! We are told that the tissues seemed to be extremely vascular and closely adherent, without any planes of section. Does that tell us anything about the pathology of the goiter? Not a great deal, because of what had been done to it. The goiter had been subjected to enough heavy radiation to give telangiectases. We used to be told by surgeons that prolonged x-ray treatment did just this. The surgeons had difficulty in operating because the goiters were extremely adherent and vascular; indeed, just like this one. The x-ray treatment

may have contributed something, although I do not blame it for everything. If they had had a bad time twice before, one would expect the cleavage planes to be gone. They had a bad time with the anesthesia. I do not mean to say that it was not excellent anesthesia, but the patient did not do well under it. I am very much intrigued with the statement about deep anesthesia. I am also interested in the fact that the respirations had to be augmented by positive pressure; they practically had to give artificial respiration. The blood pressure faded out, and they had to give the patient a lot of fluid. Maybe they gave too much.

There was a severe degree of anoxia during the operation, and although I am not certain, possibly a brain injury was sustained during the operation that was irreversible. There is a queer statement that I cannot figure out. After transfusion they say that the patient's condition was fair, and later, that he remained in coma. When did he go into coma? Did he ever come out of anesthesia?

DR. CASTLEMAN: No.

DR. MEANS: The terminal event is strongly suggestive of something intracranial. We have no examination of the fundi. We have no complete neurologic examination. We do not know whether the facial palsy was central or peripheral in type. The patient probably had increased intracranial pressure just in the hours before death, and that may be what killed him. There is no mention of a lumbar puncture.

Why did he die? I should like to suggest as a possible cause for death that he had hypoparathyroidism, and that he had had it since after the first operation, — or more likely since the second which was on the other side, — not complete but low grade. That could have caused these two attacks of stridor, and it may be that they did not know he had it when they anesthetized him. At least there is no mention of any blood chemical studies. He may have had a low blood calcium plus anoxemia, and he may have gone into a state from which he could not recover, chiefly one of brain injury due to anoxia. He had no stridor, — at least we do not know that he did, — just difficult breathing.

I posted myself a little bit on hypoparathyroidism, the effect of low calcium and so forth, and found that one can get a number of cerebral manifestations in that condition. In one case in Dr. Albright's published series,[1] there was stiffness of the right arm and leg, and partial hemiplegia. Papilledema has been described, and I therefore think that hypoparathyroidism plus anesthesia might have accounted for death. Indeed, that is my first choice, although a risky one.

The patient may have had palsy of the vocal cords. If he had had an abductor paralysis and stridor, they would have inserted a tracheotomy tube. I am interested in all this intravenous fluid they gave because if they thought he had increased intracranial pressure they would not have given the fluid. The signs of intracranial pressure appeared, and no doubt this contributed to his death.

He may have had metastases from a malignant thyroid gland. The metastatic properties of the thyroid are bizarre. I can conceive of a solitary metastasis with hemorrhage from it; but there is no way of proving that and I think that it is unlikely. He may have had hypoparathyroidism, however. They could have removed too much of the parathyroid tissue at the first or second operation.

Did he have a mediastinal mass of any kind?

DR. GEORGE W. HOLMES: I should say that the lungs and mediastinum are absolutely normal. In the lateral view the trachea does not seem to be narrow or displaced. So far as I can make out, there is nothing to cause pressure on the trachea. One other possibility is that in certain cases with heavy x-ray treatment, the trachea collapses like a bag, due to absorption of the cartilaginous ring.

DR. MEANS: I had thought of collapse, but in the record it said that the airways were perfectly good. I therefore thought that the trachea had not collapsed.

DR. JULIA ARROWOOD: The mere fact that the patient had to have artificial respiration with bag and oxygen does not necessarily mean he had anoxia — in fact, quite the contrary. He had an endotracheal tube in place and could be perfectly well oxygenated even though he was not breathing for a time.

DR. WYMAN RICHARDSON: Did he have any preoperative medication?

DR. CASTLEMAN: That morning he had 1½ gr. of Nembutal at 9:00 and ⅙ gr. of morphine and 1/100 gr. of atropine at 11:00.

DR. ARROWOOD: Again, in cases of cerebral anoxia one would expect a higher temperature than 102°F. and would not expect localizing signs on the right. Convulsions do not always occur. In 26 cases of cerebral anoxia reported by Courville[2] there was some type of muscular manifestations in all except those who died within a short time after operation.

DR. MEANS: The patient could have subarachnoid hemorrhage for all I know, but there is no neurologic evidence for it. He could have had some kind of apoplexy. He was only thirty-eight years old. Cerebral accident is a possibility.

DR. CASTLEMAN: Such as what?

DR. MEANS: Hemorrhage, either subarachnoid or ordinary cerebral hemorrhage, or thrombosis. It is all guesswork with this scanty evidence.

CLINICAL DIAGNOSES

Recurrent adenoma of thyroid.
Postoperative cerebral anoxia.

DR. MEANS'S DIAGNOSES

Nontoxic nodular goiter, adenomatous.
Postoperative cerebral anoxia.
Hypoparathyroidism?
Cerebral vascular accident?

ANATOMICAL DIAGNOSES

Multiple fetal adenomas of thyroid, with carcinomatous change in one.
Operative wound, recent: left thyroidectomy.
Cerebral embolus, left middle cerebral artery.
Cerebral infarct.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The surgical specimen removed was a nodular goiter that on section showed reddish to orange-brown nodules rather characteristic of what is known as fetal adenoma. One of these showed definite evidence of malignancy, but there were no metastases. The cause of death was cerebral, and Dr. Kubik will tell us about that.

DR. CHARLES S. KUBIK: There was an embolus in the left middle cerebral artery, with infarction of the brain in the distribution of the occluded artery. There were no thrombi in the heart to serve as a source for the embolus. Anomalous thyroid arteries are sometimes given off from the common carotid, proximal to the origin of the external carotid artery, and it seems reasonable to suppose that a clot might have been dislodged from such an anomalous vessel into the common carotid and might have been carried into the internal carotid and thence into the brain. The fact that the embolus was on the same side as the operation fits in with this theory. Microscopically the embolus consisted of very recent blood clot in which there was no organization.

DR. MEANS: Did you find any parathyroid glands?

DR. CASTLEMAN: No. The operative field was so scarred because of the previous operations and the x-ray treatment that we could not find anything that could be identified as a parathyroid gland. We cannot rule out Dr. Means's hypothesis that the patient had hypoparathyroidism, but there is no doubt that the cause of death was a cerebral embolus.

DR. MEANS: One has to explain the symptoms. It was suggested that the patient came in with recurrent attacks of dyspnea. They remain unexplainable unless the goiter caused them. It may have undergone some rapid enlargement on these occasions, with hemorrhage into a cyst. Did you find a cyst?

DR. CASTLEMAN: No.

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CASE 29442

PRESENTATION OF CASE

First admission. An eleven-year-old boy entered the hospital because of abdominal pain of six days' duration.

The patient had had measles, chicken pox and scarlet fever during his earlier life, but had been in generally good health until the age of eight. From this time on, he had numerous episodes of abdominal pain, diarrhea and vomiting. He appeared to tire easily and seemed unable to keep up with the other children. In general, however, he was in fairly good health. Six days before entry, while at a Boy Scout camp, he developed lower midabdominal pain, which was present on walking and sometimes went away in one or two hours. The pain continued intermittently until the day of admission. For the two days before entry, he had had frequent attacks of vomiting, as well as diarrhea consisting of eight or nine nonbloody, nonmucous stools daily. The day of admission the abdominal pain became constant and he had three bowel movements. There were no urinary symptoms, chills, fever or jaundice.

Physical examination showed a well-developed and well-nourished boy with a somewhat anxious expression. The heart and lungs were normal. The abdomen was flat but a dilated loop of bowel, transiently appearing at the level of the umbilicus, was seen by two observers. No masses were palpable. There was no spasm, but tenderness and rebound tenderness were present in the right lower quadrant and also referred there from other parts of the abdomen. The right testicle was not located; the left was small and high in the scrotum. Rectal examination revealed tenderness on the right.

The temperature was 98.8°F., the pulse 80, and the respirations 22.

The urine was negative. The white-cell count was 17,000. A blood Hinton test was negative.

A plain x-ray film of the abdomen showed no

evidence of intestinal obstruction. A loop of gas-filled intestine, probably sigmoid, was seen superimposed upon the pelvis.

Ten hours after admission an appendectomy was performed through a pararectus incision. The appendix appeared grossly normal. The mesenteric lymph nodes were moderately enlarged. The cecum was fairly long and minimally inflamed. The terminal ileum was normal. There was no Meckel's diverticulum. The pathological diagnosis was "healing appendix." The postoperative diagnosis was mesenteric adenitis. He was discharged on the eighth hospital day.

Second admission (two weeks later). After discharge the boy remained well for the first three days, following which he began having sharp, crampy pains across the middle of the abdomen. The attacks lasted a few seconds, with intervals of about five minutes between the attacks. The pain became progressively severer and more painful so that he doubled up with the attacks and stayed awake at night. There were two episodes of vomiting, one occurring ten days and one eleven days before re-admission. During the attacks of pain the abdomen became distended, but the distention disappeared between the attacks. The abdomen, however, became more distended during the second week. He had alternating constipation and diarrhea. In the fifteen hours before entry he had two loose bowel movements. He was seen by his physician, who observed that during the attacks of abdominal pain there were audible peristalsis and definite coils of intestine moving against the abdominal wall. He was given belladonna without relief.

Physical examination showed a greatly distended abdomen, with marked tenderness but no spasm. Moderately high-pitched peristalsis was audible. There was some tenderness in the line of the incision, which was well healed. Rectal examination revealed mild tenderness high on the right, but only slight induration; the examination was otherwise not remarkable.

The blood pressure was 110 systolic, 70 diastolic. The temperature was 101°F, the pulse 110, and the respirations 22.

The urine showed a specific gravity of 1.025; the sediment contained 1 red cell and 2 white cells per high-power field. The red-cell count was 5,460,000, with a hemoglobin of 100 per cent. The white-cell count was 9800, with 49 per cent neutrophils, which showed moderate toxic granulation. The stools were guaiac negative; and culture yielded no pathogens. The blood protein was 7.2 gm. per 100 cc., and the chloride 99.8 milliequiv. per liter. A Miller–Abbott tube passed with some initial difficulty to the upper jejunum and considerably relieved the distention. He received a 400-cc. whole-blood transfusion and daily intravenous fluid.

On the second hospital day he had two bowel movements and was quite comfortable. At that

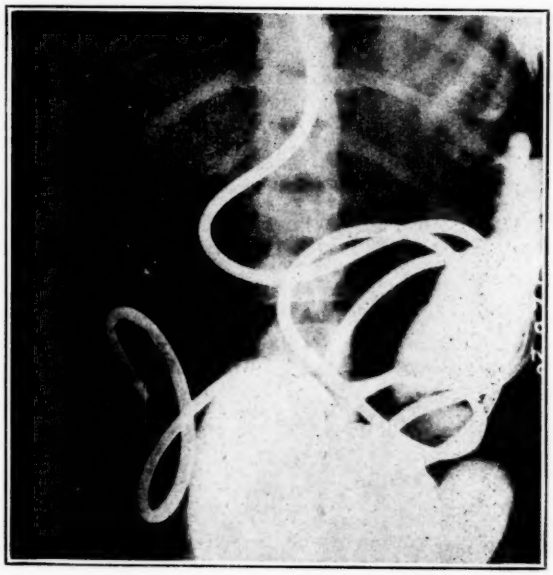

FIGURE 1. *Opaque Enema Showing Obstruction of the Colon by a Mass (arrows) below the Splenic Flexure. Note the flecks of bismuth in the dilated colon above the obstruction.*

time peristalsis was very active but "not obstructive." There was slight, constant tenderness below and to the left of the umbilicus, with rebound tenderness referred to the point of pressure. A plain film of the abdomen showed a loop of dilated small bowel in the right upper quadrant. There was gas within the colon. The right side of the colon contained flecks of opaque material, apparently representing bismuth. One day later the opaque material had moved to the region of the splenic flexure . At that time the tip of the Miller–Abbott tube was at the ileocecal valve, and the small intestine was deflated. An intravenous pyelogram was negative.

On the third day the boy vomited 50 cc. of fluid and had two loose bowel movements. The Miller–Abbott tube was draining fecal material, which frequently plugged the tube. He was not distended. The temperature was 100.5°F. and the pulse about 100. On the fifth day the temperature rose to 103°F. He had crampy abdominal pains, vomited once and had one bowel movement. One hundred cubic centimeters of stomach contents was aspirated with apparent relief.

A plain film of the abdomen showed the Miller–Abbott tube to be in the third jejunal loop. In

the left upper quadrant there seemed to be a mass pressing the colon laterally and deforming it. Neither the left kidney shadow nor the psoas contour could be made out. Some indefinite mottling was seen in this area, which could have been in the large distended colon or in the mass. One dilated loop of fluid-filled bowel was present, but it was impossible to say whether this was large or small intestine. There were several loops of small bowel that contained gas but were not greatly dilated. A barium enema showed the opaque material to pass quite readily to the proximal descending colon, where an obstruction was encountered. The colon was compressed laterally against the abdominal wall, and there was a defect medially about 5 cm. long, over which the bowel was ragged and irregular. On one film there appeared to be an annular constriction which, however, was not seen on a subsequent examination.

An abdominal exploration was performed on the seventh hospital day.

Differential Diagnosis

Dr. Oliver Cope: The record evidently does not give the confusion that the clinical picture did at the time; to me the record on certain points is clear. I am struck by the fact that an intravenous pyelogram was done. At the second admission the kidney was again investigated. I wonder why so much attention was given to the kidney.

The child suffered from intermittent intestinal obstruction — that much seems to be clear. The second point that is clear is that the appendectomy did not cure him, in other words, the disease was not appendicitis. The third feature is that the correct diagnosis was not made at the time of the first operation. Perhaps the operator observed more than is given in the record, but one thing is important — namely, that he noted minimal inflammation of the cecum. Such inflammation in the presence of a normal appendix and signs of intermittent intestinal obstruction perhaps should have been diagnostic. It is difficult to be sure but it is possible that the surgeon who operated on the patient at the first operation failed to make a diagnosis when he could have. The other thing that the surgeon should have noted, if possible, having observed inflammation of the cecum and a normal appendix, is whether the cecum was attached by a loose mesentery. I get the impression that the cecum was fairly long. We ought to have a more accurate description of that in anatomic terms. I suppose it means that the cecum was on a loose mesentery. In addition we should have been informed whether the large bowel was palpated and whether it was properly rotated. If a segment of large bowel had an ample mesentery it suggests that rotation may not have been complete.

After the first operation intermittent obstruction recurred, and the episodes on the second admission sound to me like obstruction, with beginning impairment of circulation of part of the bowel, causing a rise in temperature and an increase in the illness of the patient. The diarrhea fits with such a point of view. It is interesting that there was no blood in the stools.

Dr. Benjamin Castleman: One out of four stool examinations showed a ++ guaiac test.

Dr. Cope: That is reasonable. It would be unusual, I believe, for intussusception to exist as long as the final episode did without some blood in the stools. There are two diagnoses in my mind that fit the entire picture. The commonest one is intussusception. Although the x-ray picture is consistent, perhaps we should get the details from the X-ray Department before being too flat-footed about it. It would be unusual, however, not to find a mass palpable in the abdomen if the intussusception started at the ileocecal valve and telescoped enough of the large bowel to bring the mass into the left upper quadrant. The X-ray Department found a mass, but it was not felt on physical examination.

The other diagnosis that I think is the only other plausible one — perhaps I am being far too hasty — is torsion of a partially rotated large intestine. The x-ray examination suggests at one place that there is a large gas-filled loop, which is the usual accompaniment of torsion. Torsion is a less likely diagnosis than intussusception but one that could occur and cause obstruction at the splenic flexure. Both these lesions may form and relieve themselves and therefore may recur intermittently. It is only when the intussusception becomes advanced enough so that it cannot reduce itself, or when the torsion has been present for some time, that impairment of the bowel wall occurs.

Dr. Milford Schulz: In the barium enema you can see an obstruction just below the splenic flexure. The colon is displaced laterally against the abdominal wall, and there is a constant defect, which is 5 or 6 cm. in length. The defect is not suggestive of an intussusception, since you can see fairly distended colon just above the area of obstruction, visualized by the bismuth that had previously been given as medication. Here is the annular constriction. Here it is on another examination. Something is fixed to the soft tissues, displacing the colon laterally. The impression at the time of examination was that it should have been a carcinoma, but in view of the boy's age a

compromise diagnosis of either lymphoma or an inflammatory lesion was suggested. The pyelogram was done because of the possibility of a retroperitoneal inflammatory process.

DR. COPE: The x-ray films are impressive. When I read the record I did not get the slant that I do now from your recounting and pointing out the characteristics of a malignant tumor. The thing that may be the red herring is the observation of inflammation of the cecum at the first operation. Such inflammation should mean either torsion or intussusception that had relieved itself.

Could an intrinsic lesion of the bowel explain the x-ray findings?

DR. SCHULZ: Yes, I think it could.

DR. COPE: May I ask for the confines of the mass described? Could it be accounted for by inflammation outside the splenic flexure?

DR. SCHULZ: Here you see the mass in the left upper quadrant with some mottling within it. It may be a distended colon with gas and fecal material, or it may all be extrinsic to the colon, perhaps with some necrotic material within it. I might say in passing that the x-ray appearance of intussusception is usually quite characteristic.

DR. COPE: Intussusception may result from a tumor so that the obstruction of the bowel becomes complete only when intussusception occurs. There is nothing in the history that excludes the presence of a large polyp or tumor that gave some mechanical difficulty resulting eventually in obstruction. The patient certainly had intestinal obstruction. We have some evidence of a mass or tumor by x-ray, which, if that were the primary agent of the obstruction, ought to have resulted, not in intermittent obstruction, but in permanent obstruction. It is possible that the episodes before the first operation were the initial phase of obstruction, over a period of months, and resulted in final obstruction at the time of the second admission. I am still impressed by the story of the intermittent character as it is given in the record and by the fact that the boy was apparently relieved of obstruction at the time of the first operation. Therefore, I shall stick to the idea of either intussusception or a volvulus of the large intestine in the absence of more positive evidence of intrinsic tumor. In the absence of the positive x-ray finding of intussusception, I am inclined, leaning heavily on the "loose" cecum, to make a diagnosis of volvulus of the large bowel with some degree of necrosis, possibly going on to abscess formation to account for the x-ray finding.

DR. SCHULZ: Does not a loop of bowel with volvulus usually contain a lot of gas?

DR. COPE: That is true. The two cases of volvulus of the right side of the colon that I remember vividly both had a big bolus of gas in the cecum. That was not found here, but in neither of my cases had the bowel been decompressed from above by a Miller–Abbott tube. We have evidence from the history that the Miller–Abbott tube had decompressed the small and large bowels, and fecal material had drained through the tube. So one would not necessarily expect to find a distended bowel proximally.

DR. ROBERT R. LINTON: How often does volvulus occur in a child of eleven? Volvulus of the large bowel has always occurred in older patients as I remember it.

DR. COPE: Some of the house staff may remember a physician who, at the age of thirty, had a volvulus of the right side of the colon. He had undoubtedly had intermittent attacks of the volvulus since the age of six. After one, the appendix had been removed. The story was much like this one only it lasted over a period of many more years. The doctor's father told me that when the attacks occurred in childhood, the boy would get down on his hands and knees suffering from intense colic and try to defecate. After an hour or two of rolling around the attack would be relieved. When he first came to us the attack had lasted three days — much longer than any previous attack. He had a volvulus with gangrene of the bowel and had a stormy time from generalized peritonitis. If one makes a diagnosis of volvulus in this boy, one has to assume that there was necrosis of the bowel to account for the increasing septic appearance of the chart and also for the x-ray findings.

DR. CASTLEMAN: If volvulus had been present all this time, do you not think that it would have been seen at the first operation?

DR. COPE: Volvulus could not have been present all this time. It would have to have been intermittent. The patients I have seen with intermittent volvulus or intussusception have had appendectomies following an attack and the correct diagnosis was not made at the first operation. I imagine it may be a difficult thing to recognize.

DR. FRANCIS MOORE: The surgeon who performed the first operation was no more satisfied with his findings than Dr. Cope is. He felt that the appendix did not account for the picture. At the second operation the boy was operated on through an incision in the left upper quadrant, because of the x-ray findings. The splenic flexure was found to be virtually totally obstructed by a large, ragged, hard, infiltrating, obviously neoplastic mass, which was mostly on the medial side of the bowel, with some on the lateral and posterior aspects and ex-

tension down along the aorta and vena cava. It did not look like an intrinsic bowel tumor. At that time biopsy of two or three lymph nodes was done, but frozen section was inconclusive. The only thing that could be done was to relieve the obstruction; hence an enteroenterostomy around the lesion was performed, anastomosing the transverse colon to the sigmoid.

Clinical Diagnosis

Intestinal obstruction.

Dr. Cope's Diagnosis

Volvulus of large intestine?
Intussusception?

Anatomical Diagnosis

Colloid carcinoma of colon.

Pathological Discussion

Dr. Castleman: The biopsy showed a characteristic colloid carcinoma.

Dr. Linton: What was the grade of malignancy?

Dr. Castleman: Colloid carcinoma of the bowel is extremely malignant. I think that it is commoner in children than is adenocarcinoma. I can recall one other case of colloid cancer in a child of seven or eight, who came in with a mass in the groin that proved to be a metastasis from a cancer of the sigmoid.

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NATIONAL RESEARCH COUNCIL ON FOOD RATIONING

Soon after the inauguration of a point system of food rationing in March, 1943, the director of the War Food Administration requested the National Research Council to appoint a committee of physicians to advise on special dietary needs and the best method of meeting them. This group was organized, with Dr. William D. Stroud, of Philadelphia, as chairman, within the Division of Medical Sciences of the council, as the Subcommittee on Medical Food Requirements under the general jurisdiction of the Committee on Drugs and Medical Supplies, of which Dr. Walter W. Palmer, of New York City, is chairman. The recommendations of this committee have been published in the October 16 issue of the *Journal of the American Medical Association*.

Food rationing is recognized as a vexing problem, particularly so in a food-producing country such as ours, a country geographically immense, with extremes of climatic conditions, with dietary habits varying in different sections and among certain racial components, with geographical variations in food availability and distribution, and with many important food groups still unrationed. The recommendations of the subcommittee cover these qualifying factors, without attempting to "provide an exclusive compendium of conditions in which extra rations are thought medically indicated." It is further stated, "They [the recommendations] are rather a guide to the vast majority of such conditions, any attempt to define all of which would vitiate the scientifically necessary flexibility inherent in any wise system of rationing for the sick." Recognition has been made of the precedent established by the Food Rationing Advisory Committee of the British Medical Research Council, which acts in an advisory capacity to the Ministry of Food. In England, however, the problem is actually somewhat simpler owing to stricter rationing of a more limited supply of food, practically all of which is owned by a governmental agency of a geographically small and cohesive nation.

The recommendations of the subcommittee call for the restriction of the authority to certify patients to "persons licensed to practice medicine and surgery in their respective states," for appeal committees of qualified physicians, for the annual renewal of certification, and for certain maximal allowances in specified diseases, notably diabetes mellitus, tuberculosis, chronic nephritis of the nephrotic type, cirrhosis of the liver, severe hepatitis, chronic ulcerative colitis, chronic suppurative diseases and sprue. The diagnosis of chronic ulcerative colitis or of sprue is not accepted unless certified to by three physicians.

It is scarcely necessary to reiterate that food rationing constitutes a vexing problem. Processed foods present such a variety of types, from fruit juices that are mostly water to dried vegetables containing none, that it obviously makes little sense to measure them with the same yardstick or to weigh them in the same scales. The reason for grouping meats and fats is certainly one of organizational convenience that is not based on sound dietetic principles. Furthermore, a reasonably good sustaining diet can be built up of unrationed foods alone — when they are available.

In Massachusetts the policy of having a medical advisory committee to the state branch of the Office of Price Administration was adopted early in the summer, and this committee adopted the principle that, although it might be its brother's keeper, it did not wish to exercise police control over him. If a registered physician of Massachusetts wishes to employ dietary measures for the treatment of a patient and does so within reasonable limits and with apparently honest intent, the advisory committee will give him its support — nor does it challenge its colleagues' intellectual integrity by demanding the certification of three physicians for any diagnosis.

In our current years of trial, the more that can be accomplished by education and by mutual understanding and co-operation, the sweeter will be the taste of our ultimate success. It will be an unfortunate outcome if victory over our external enemies has to be won at the cost of increasing regimentation, coercion and force at home.

THE CHILDREN'S CENTER

THE Children's Center of Boston has now been in operation for over nine months, and the occasion seems suitable to review briefly its auspices, its purpose, its program and its accomplishments.

The Center was established in Roxbury, near a low-income community, in January, 1943, under the auspices of the Judge Baker Guidance Center and aided by a grant from the Rockefeller Foundation. It was set up, however, as an independent organization, with its own staff under the direction of Dr. Marian C. Putnam and Mrs. Beata Rank. Its purpose was to provide day-nursery care and psychiatric consultation and treatment for infants and preschool children — a service that is almost unique, since the opportunity to begin educational and therapeutic guidance has hitherto rarely been offered in those family situations where emotional conflicts have appeared as early as the first or second year of the child's life. It is obvious that the best results can be obtained in these most formative years, and before unfavorable parent-child relations have become fixed.

The Center offers and has been furnishing a five-point program: day-nursery care, which is open to a group of thirty to thirty-five children with an age range from infancy to five years; in-patient care for a few children whose residence at home is temporarily inadvisable; therapeutic and educational work with parents and children; a consultation service available to the whole community; and facilities for the training and teaching of students in the various fields of child care. In this last respect, teaching programs are being offered for various professional people — social workers, nursery-school teachers, volunteers and students in child care and, ultimately, psychiatrists and pediatricians. A special grant from the Rockefeller Foundation helps to open the opportunity for study and research.

As evidence of the need that the Center is meeting and of the progress already made, it is interesting to note that during its first half year of existence applications were received for nearly 250 children. These came from thirty-seven agencies, from private physicians and through direct neighborhood contacts.

This new and valuable organization is particularly welcome in a community that, already richly endowed with them, knows how to utilize and appreciate its many health and social agencies.

MEDICAL EPONYM

Hurler's Syndrome

Although the term "gargoylism" as applied to this syndrome was first used by Ellis, Sheldon and Capon in an article entitled "Gargoylism (Chondro-Osteo-Dystrophy, Corneal Opacities, Hepatosplenomegaly and Mental Deficiency)," which appeared in the *Quarterly Journal of Medicine* (**29:** 119–135, 1936), the source of the eponym is an article by Dr. Gertrud Hurler of the University Children's Clinic in Munich. Dr. Hurler wrote "Über einen Typ multipler Abartungen, vorwiegend am Skelettsystem [Multiple Degenerative Changes, Predominantly Skeletal]," which appeared in *Zeitschrift für Kinderheilkunde* (**24:** 220–234, 1919). A portion of the translation follows:

> In the foreground of the clinical picture presented by our little patients stands the peculiar deformity of portions of the skeleton, namely of the head as a whole and especially the occipital region, of the clavicles, of the proximal end of the humerus and of the scapula. As the x-ray pictures show, we are dealing with changes in conformation particularly through extensive hyperostoses and defects (gaping sutures) in the skull, apparently the result of disturbances in ossification. The clavicles give the impression of being heavy, massive, excessively cured bony structures. The substance of the scapula seems very compact, the acromion markedly bulging, the joint socket shallow and small. In addition there is in both children a marked kyphosis, in one a funnel breast, in the other a pigeon breast, and in both, diffuse clouding of the cornea pronounced by the eye specialist to be hydrophthalmia, that is, a congenital defect; and as further stigmas of degeneration there are in both children crooked little fingers and contractures of the fingers.

R. W. B.

CORRESPONDENCE

BOOK REVIEWS

To the Editor: In view of the recent critical review of the book, *Surgical Practice of the Lahey Clinic*, I would like to make two suggestions which, I believe, are constructive in character. These relate not only to this review but also to others to be published in the future.

This review is published anonymously, as has always been the custom of the *New England Journal of Medicine*, and my first suggestion is that all reviews be signed. This is but simple justice to the author and the publication, will make the reviewer more conscious of his responsibilities, and will permit readers to decide (1) whether the reviewer is a qualified critic and (2) whether his criticism might be colored by personal prejudice.

The second suggestion is less important. Since a review, to my mind, gives an opinion as to the value of a book, it should be presented to the reading public soon after publication. This review of *Surgical Practice of the Lahey Clinic* appeared two years after publication, and after it had been, according to the W. B. Saunders Company, among the best selling books for the year of publication.

The book is composed, as is stated in the preface, of a group of selected papers previously published. These were written by a busy and often overworked staff of surgeons, fellows, anesthetists and other specialists in the Clinic, with a desire to share with other members of the medical profession the methods they had found useful. The authors would be the first to admit that the book is not what might be described as a literary gem. However, its enthusiastic reception, as evidenced by the large circulation and the many complimentary letters from purchasers, indicates that it has pleased many readers and apparently has answered a definite need.

As to the reviewer's comparison of the American and British literary style, it is probably true that the criticism so often leveled at us of being too utilitarian is also true of our literary style. However, we are Americans, and our literature is read largely by Americans. Today our American utilitarian methods are serving us and our respected English allies to an extent that is gratifying to them and to us.

As surgeons we are interested primarily in saving lives and limiting suffering. Secondly, we are interested in presenting our experiences to others to accept or to reject according to their judgment and trust in us.

Frank H. Lahey, M.D.

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WAGNER–MURRAY–DINGELL BILL

To the Editor: The time has come once again when it appears to me that one from the ranks should speak out frankly.

What I have in mind is the present approach in the way of argument in opposition to the Wagner–Murray–Dingell Bill, and similar proposals now before Congress.

It seems to me that any physician listening in on the "Forum of the Air" discussion of the evening of September 22, must have realized how much damage is done to the present methods of supplying medical care to the public by such forms of argument, either for or against the proposals. To my mind our leadership is weak in debate. The points presented are not persuasive. Brilliancy of discussion is evident in full measure, but such points of view as are presented are antagonistic to the public. They gain us nothing in the way of support. On the contrary, they repel. Under such circumstances, one cannot fail to come out of the discussion with ignorance and prejudice, especially if there is profit in prejudice, without recognizing defeat.

The arguments of our leaders concern themselves with admitting gross defects. Our spokesmen seek sympathy and protection under the wings of our enemies. We pander to corporate practices of medicine, admitting that such practices are desirable. We strive to show that the bureaucratic groups are correct, and that we ourselves are attempting to do the very things that they propose. Therefore, we are now agreeing that they have been right all along, and that we have been wrong — that we are trying to do the same thing that they are trying to do,

and that we have been at fault. Such admissions are weak, nonconstructive and damaging.

Throughout recent years, when this problem has been acutely before us, I have adopted a very simple method of handling the situation insofar as the question has arisen amongst my personal contacts. I think that it has been practical, and I know that it has, in every case, been effective. Almost all the public are in favor of any method that will give them service at lower rates. They usually start off by telling me that they think it would be a wonderful thing. I agree with them, and add that it might work quite well for the medical profession. I point out that physicians have been donating services through clinics and hospitals to the extent of probably $500,000,000 annually and that, in addition, poor collections in private practice virtually constitute a gift to the public of another enormous sum of indeterminate amount. I add that, if the Government or others took over the furnishing of medical care to the public, the doctors would be paid for all these present-day charity services. I tell them that, from a financial point of view, governmental supply of medical services might, and probably would, be a better thing for the doctors, since they would be compensated for these present charities by funds derived from taxation. I invariably find that the people who started off the conversation change their minds. They do not want anything like that if the doctors are going to profit or be paid by taxation or otherwise. They have come to think of doctors as public servants that should be poorly paid, or not paid at all. They tell me that they never thought of the matter from that angle. They are invariably converted, since they apparently are opposed to anything that will pay the doctors at any expense to themselves. Obviously, they were led to believe that they were going to get something for nothing.

Then on top of that I point out that many of the hospitals throughout the world have been provided through voluntary contributions by well-to-do citizens and that the Red Cross and other such organizations are likewise supported largely by voluntary contributions. I add that, if the Wagner–Murray–Dingell Bill or any similar bill went through Congress, these organizations would have to pass out of existence, insofar as control and voluntary contributions are concerned, and that they then would become a burden on the taxpayer.

I find that the public does not want state medicine under those terms, and it appears to me that some such general approach to the problem would be far more effective than the present one.

I do not believe that any businessman would argue his case in the way that our leaders are presenting their cringing arguments. He would approach the argument in a businesslike way. Looking for sympathy engenders only scorn. Admitting that we are wrong when we are not wrong, showing weakness when strength of argument should be our method, pandering, flattering and crawling, all seem to me to be the surest possible road to defeat. I believe that such methods have assured the passage of the Wagner–Murray–Dingell Bill during this session of Congress by an overwhelming majority.

Why not face facts squarely? I have no desire to sit here pounding out my heart and thoughts for publication in any wish for recognition as a leader. I desire no responsibility. But, it does stir up my wrath when I listen to such weak arguments, and see such bad leadership as our spokesmen have given through these years in so many ways — leadership that is directing us straight into the path of defeat. Surely, some of us must have guts enough to come out squarely in such times, in order to try to let us see things straight and find a better way.

W. A. Hutton, M.D.

Palmer, Mass.

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

The first fall meeting of the New England Pathological Society was held in the auditorium of Boston University School of Medicine on October 21.

The first paper of the evening was "Immersion Foot and Allied Disorders" by Dr. Carl K. Friedland. Cooling the extremities of man to 15 to 18°C. causes simple vasoconstriction. Further cooling to, but not below, the freezing point results in tissue injury, an increase in capillary permeability and exudation of plasma into the tissues. Chilblain, pernio, trench foot and immersion hand and foot are all fundamentally due to the same pathophysiologic process, their apparent differences being the resultant of the site, type and duration of exposure. Other factors such as dependency, immobility, maintenance of body temperature and cold sensitivity also tend to modify the picture. Frostbite is designated as a separate entity because it is due to actual freezing and ice-crystal formation within the tissues.

In the discussion that followed Dr. Shields Warren described cases of prolonged immersion in which, after one and a half to two months, evidence of a mild to moderate Wallerian degeneration in the peripheral nerves was still present with an ultimate fair degree of recovery, although in one patient after six months a trophic ulcer due to anesthesia of the toe developed. In later periods there was pain thought to be due to fibrosis about the nerves. He also stressed the importance of the edema seen in this condition, which results in an increased amount of collagen with hyalinization so that the histologic picture simulates long-standing elephantiasis. The small arteries often show complete occlusion by old fibrous tissue, sometimes with recanalization consistent with the end result of thrombosis. Dr. Valy Menkin raised the point whether the substance responsible for the physiologic changes was due to histamine or a histamine-like substance. He believes that the changes are caused by a leukotaxin resulting in increased permeability, and cited experiments in which the exudate found in the tissues was dialyzed and the histamine-like substance and leukotaxin were removed. When this fluid was resynthesized with histamine, there was no change in capillary permeability. If the fluid was resynthesized with leukotaxin, the original effect was produced. He also raised the question of a neurogenic effect on the development of the inflammatory reaction. Dr. Moritz raised the question whether there were individual tissue specificities to thermal injuries, and in the discussion Dr. Warren brought out the point that the endothelium of the capillaries, small venules and lymphatics showed the earliest signs of injury, and he stated that he believed that this was the most susceptible tissue. Dr. Stanley E. Bradley presented the second paper,

"Blast and Crush Injury During Warfare." Extended naval operations and the bombing of crowded cities during the present war has aroused considerable interest in the immediate and remote clinical effects of the detonation of high explosives. Analysis of the physical character of an exploding charge indicates that the formation of a rapidly moving, high-compression wave front or "blast" may result in serious injury or death, on land or in the sea, unattended by marks of external violence. The syndromes of "blast lung" and "water blast" have been delineated and studied experimentally. In addition to the banal aspects of injury secondary to an explosion of any type, prolonged compression of the limbs by wreckage, with subsequent renal damage and uremia, has been seen fairly frequently and has inspired exhaustive experimental study. Renal functional changes during traumatic shock with special reference to the "crush syndrome" were briefly outlined.

In discussing the paper Dr. Menkin raised the question whether there was elevation of glucose, the result of glucogenesis from injured tissue, and whether the entire problem was related to the euglobulin fraction of the exudate—either euglobulin itself or a fraction, necrosen, causing particular injury to the liver and kidneys. The author's answer was that the carbohydrate metabolism was not altered; there was variable but usually insignificant adrenal damage, with no evidence of liver damage. The question was raised whether a subdural hematoma could be produced by blast injury alone. In the discussion it was brought out that most cases of subdural hematoma were the direct result of trauma secondary to the blast pressure.

The last paper was presented by Dr. Robert W. Williams on the subject "Aviation and Cardiovascular System." In aviation the cardiovascular system must withstand two principal strains: centrifugal force due to sharp turns at high speed and low barometric pressure due to high altitudes. Centrifugal force in modern fighter planes may exceed eight times the force of gravity (8*g*). The vascular system in the dependent parts of the seated pilot is distended by blood under this tremendous force until there is insufficient blood circulating to the head. This causes visual blackout and then unconsciousness. The effects of centrifugal force may be counteracted by various mechanical devices that tend to prevent the pooling of blood in the lower parts of the body. At high altitudes the barometric pressure decreases until at about 50,000 feet it falls below the partial pressure of alveolar carbon dioxide and water vapor. Therefore at this altitude, even with 100 per cent oxygen supplied by mask, life is impossible; only with a pressurized cabin can man survive. Even at lower levels anoxia is proportional to altitude and causes not only central nervous but also cardiovascular pathophysiology. In addition, at altitudes above 18,000 feet, nitrogen dissolved in the tissues comes out of solution and may collect as bubbles. The symptoms of the "bends," whether articular, pulmonary, cardiovascular or central nervous, depend on where these bubbles appear. The bends can be prevented by prebreathing oxygen, or better, by using pressurized cabins.

In discussing the paper the question was raised whether it is possible to train groups of aviators to tolerate these effects of centrifugalization. It was Dr. Williams's opinion that this was not possible.

BOOK REVIEWS

Standard Nomenclature of Disease and Standard Nomenclature of Operations. Edited by Edwin J. Jordan, M.D. 12°, cloth, 1022 pp. Chicago: American Medical Association, 1942. $4.00.

This volume, *Standard Nomenclature of Disease*, first published as a book in 1933, revised in 1935 and now completely revised, is combined with *Standard Nomenclature of Operations*, first published in June, 1942.

The basic plan used for the work was adopted officially at the second National Conference on the Nomenclature of Disease. In 1937, periodic revision was taken over by the American Medical Association. In connection with the third edition, a fourth National Conference on Medical Nomenclature was held under the auspices of the American Medical Association in Chicago in March, 1940, with Dr. Haven Emerson, of New York City, serving as chairman. The present edition is the result of this conference. There is no essential change in the arrangement of the material in this edition; however, about thirty-five hundred additions, deletions and corrections have been made in individual diagnostic entries. The entries in the section "Disorders of Endocrine Glands and Hormones," which appeared in the classification "Body as a Whole" in previous editions, have been reclassified under the appropriate organs. The present edition is authoritative, since it represents the consensus of about sixty delegates to the conference from interested organizations and institutions.

Following the classification of disease, there is an extensive index referring to etiologic classification, and a useful table of eponymic diseases is appended. The aim of the work is to include every disease that is clinically recognizable and to avoid repetition and overlapping. English terms are employed, whenever possible, in preference to Latin or Greek terms, although numerous exceptions occur, especially under diseases of the skin and of the eye.

The method of classification is based on two primary factors: the portion of the body concerned (topographic) and the cause of the disorders (etiologic). These two elements are designated by numerical digits separated from each other by a hyphen. The first three digits in the disease code describe the topographic site; the last three, following the hyphen, describe the etiologic agent.

The nomenclature of operations was compiled as a parallel to the code of disease in response to a demand from various sources. The compilation is a combination of all well-known operative terminologies of various hospitals and associations. The division of fundamental surgical procedures into eight main categories was carried over, to a large extent, from the *Classified Nomenclature of Operations* of the New York Hospital. This code attempts to bring about standardization in designating operations. It likewise has a complete index referring back to the various operations. All hospitals and others concerned with scientific medicine should adopt a standard nomenclature, particularly if they do not have a complete schedule of their own.

This book constitutes a standard reference source. It should be in the office of every surgeon and physician, especially those who are concerned with hospital service.

Borderlands of Psychiatry. By Stanley Cobb, M.D. 8°, cloth, 166 pp., with 28 illustrations. Cambridge: Harvard University Press, 1943. $2.50.

Dr. Stanley Cobb, now psychiatrist-in-chief at the Massachusetts General Hospital, has long been a student of the borderlands of psychiatry. Beginning as a neuropathologist, with neurophysiologic leanings, he first became a neurologist, later an experimentalist and finally a psychiatrist. He has, during these years, wandered widely in the fields of the psychoneuroses, epilepsy, the organic disorders of the central nervous system, alcoholism and speech defects. This borderland, or to most psychiatrists the hinterland, contains, according to Cobb, a population of six million people, a vast number when compared with the six to seven hundred thousand who make up our hospital population for mental diseases, the primary field used for the major training center of most psychiatrists. With Cobb's background, therefore, physicians have long awaited the Lowell Lectures given by him in 1940. They will not be disappointed in this book, a somewhat elaborated and expanded text, geared to a more medical audience than usually attends a popular-lecture series.

Much of Cobb's training and fundamental thinking comes out in this book. He soundly views each field of the borderland, carefully evaluates the acreage, the quality of the soil, its previous history, its presumptive yield and its crop prospective in view of future tillage. Much of the field has been previously explored, such, for instance, as the old body-and-mind problem, now fertilized and revitalized as psychosomatics. Cobb presses and strains out the essentials in a brief, penetrating manner, leaving one sure of the way he feels, and almost certain that he is essentially right in his deductions. At least his review is based on a thorough study of each subject, neglecting no aspects, be they physiologic, anatomic, psychologic or psychiatric.

The whole book makes one think of a New England boiled dinner. There are many ingredients, all well cooked and furnishing sound, hearty fare. But one cannot digest quickly such varied provender as "the parallel evolution of speech, vision and intellect," "the function of the frontal areas of the human brain," "the anatomical basis of the emotions," "consciousness" and "concerning fits." Taken in small pieces, chewed and ruminated, each portion makes a tidy meal, and one well worth the time. Some psychoanalysts may not favor their portion, but neither will all the structuralists nor all the behaviorists. The meal, however, is excellent and everyone will find something at the table to his liking. If he does not, he had better go hungry.

The style of writing leaves something to be desired. Cases are treated "from more than one angle"; "cryptogenic" is discarded, as being a "long" Greek word, although Cobb does not hesitate to use "dysrhythmia," "anosognosia" or "strephosymbolia." Graves's name is constantly misspelled, as is that of Lorente de Nó and J. F. Fulton. There is a good index to the book, and selected references at the end of each chapter. The reviewer cannot conceive how anyone could not find both nourishing and thought-provoking sustenance in this stimulating, well-organized monograph. It is hoped that in future editions the textual errors will be erased.

Psychosomatic Medicine: The clinical application of psychopathology to general medical problems. By Edward Weiss, M.D., and O. Spurgeon English, M.D. 8°, cloth, 687 pp., with 2 tables, 9 illustrations and 4 charts. Philadelphia and London: W. B. Saunders Company, 1943. $8.00.

The old body-and-mind relation takes on a fresh aspect when, in modern times, it becomes "psychosomatic medicine." A periodical, first issued in January, 1939, with the designation *Psychosomatic Medicine*, was the early effort in the field. Now comes a book, stemming from the same impulse. The senior author learned about twenty years ago that one patient's illness, the chief symptom being headache, "was her infantile way of expressing disapproval of her brother's marriage and, when the meaning of the illness was made clear to her, she promptly recovered." Now he finds that similar cases are by no means the exception in the practice of medicine. Many authorities, he states, agree that cases like the above constitute about a third of all practice, and that another third concern patients who have emotional factors complicating and adding to the burden of their physical disease.

This book deals with the problems of the emotional factors in the cause or augmentation of illness. The volume stresses personality development and the establishment of psychopathology early in life. In a series of chapters, each division of the body structure is taken up in detail. The gastrointestinal and cardiovascular systems, as might be expected, receive most attention, but the endocrine, special-sense and the genitourinary systems are not neglected. There is a brief chapter on military medicine, a timely effort but somewhat out of place in this volume, and four final chapters on treatment.

In the opinion of the reviewer, the book presents a mass of data, somewhat poorly evaluated and often presented without ordinary scientific discrimination. Many case histories are used, but they are often feeble arguments for positive generalizations. As in the case noted above, all symptoms tend to disappear only too quickly once the inner springs of discord are touched. In other words, the authors make happy endings almost as frequent as in motion pictures, a goal seldom reached in the practice of most psychiatrists.

In spite of these shortcomings, the book offers much thoughtful material for medical students and practitioners. It at least brings forcibly to their attention one of the most pressing problems in medicine today. The authors demonstrate that the emotions may play a role in illness, as in our daily lives; what they fail to show in an entirely convincing manner — possibly the time is not ready to show it — is how that role is played. From time immemorial emotions have colored our lives; this book leads one to believe that the coloring early in life is of greater importance in disease than any coloring that may come later and that many illnesses, the result of pathologic changes, come as the result of the emotional strain. Although there is some evidence that such statements may be true, much more must be known before a broad generalization can be made. This book forms part of the stimulus that arises from an awakened interest in psychosomatics and, as such, deserves a wide reading.

(Notices on page xii)

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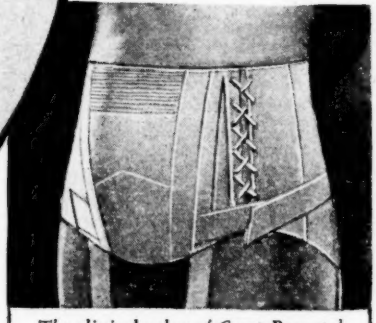

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NOTICES

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Amphitheater of the White Building, Massachusetts General Hospital, on Wednesday, November 17, at 8 p.m.

PROGRAM

A Classification of Hypoestrinism. Dr. Fuller Albright.
The Physiology of the Hormone Relaxin. Dr. Frederick L. Hisaw.
Proteins in Nutrition. Dr. Fredrick J. Stare.

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Beth Israel Hospital on Thursday, December 2, at 12:00 m. Dr. Samuel A. Robins and his associates will discuss "Radiology of the Alimentary System."

TUFTS MEDICAL ALUMNI LECTURE

An alumni lecture will be given at Tufts College Medical School on Wednesday, November 17, at 4 p.m. Brigadier General Raymond W. Bliss, M.C., A.U.S., Washington, D. C., will speak on "Plans and Operations of the Surgeon General's Office."

Physicians and students are cordially invited to attend.

(Continued on page xv)

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SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, November 11

Thursday, November 11

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

Friday, November 12

*9:00–10:00 a.m. Head Injuries. Dr. Houston Merritt. Joseph H. Pratt Diagnostic Hospital.

Saturday, November 13

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, November 15

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, November 16

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department. Massachusetts General Hospital.

Wednesday, November 17

*9:00–10:00 a.m. Some Experiences in the Canal Zone and Central America. Comdr. William M. Shedden. Joseph H. Pratt Diagnostic Hospital.

Fall meeting of the New England Oto-Laryngological Society. Massachusetts Eye and Ear Infirmary.

*12:00 m. Clinicopathological conference. Children's Hospital.

*4:00 p.m. Plans and Operations of the Surgeon General's Office. Brigadier General Raymond W. Bliss. Tufts College Medical School.

8:00 p.m. Boston Society of Biologists. Massachusetts General Hospital.

*Open to the medical profession.

December 2. Boston Gastroenterological Society. Page xii.

December 9. Treatment of Allergy. Dr. Francis M. Rackemann. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

February 12. American Board of Obstetrics and Gynecology. Page ix, issue of October 28.

District Medical Societies

SUFFOLK

December 2. Censors' meeting. Page x, issue of September 16.

WORCESTER

December 8. Worcester City Hospital.
January 12, 1944. Memorial Hospital, Worcester.
February 9. Worcester State Hospital, Worcester.
March 8. St. Vincent Hospital, Worcester.
April 12. Hahnemann Hospital, Worcester.
May 10. Annual Meeting.

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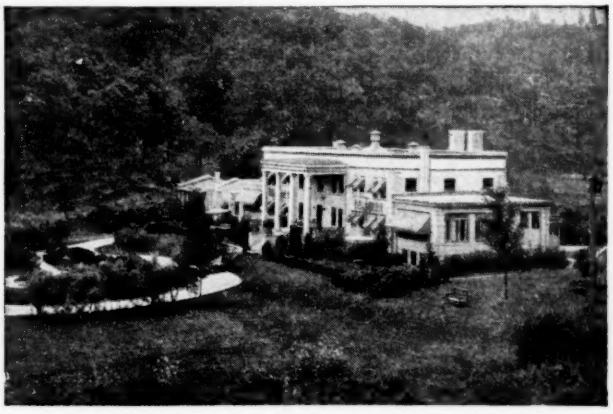

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